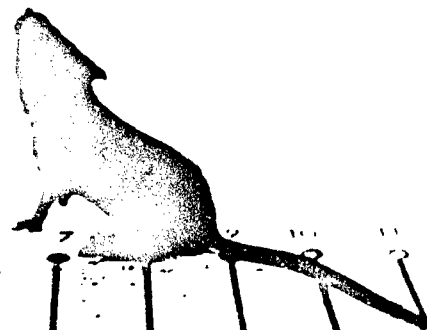


II. INTERNATIONAL SYMPOSIUM ON
**GENETIC CONTROL OF
HOST RESISTANCE TO
INFECTION
AND MALIGNANCY**

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Montreal, Canada
May 12-16, 1985

AD-A163 002

PHOTOGRAPH THIS SHEET

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**II INTERNATIONAL SYMPOSIUM ON
GENETIC CONTROL OF HOST
RESISTANCE TO INFECTION
AND MALIGNANCY**

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Research Institute

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and Infectious Diseases

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Allergy and Infectious
Diseases

ACKNOWLEDGEMENT

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Medical Research Council of Canada
National Institutes of Health
Fonds de la Recherche en Santé du Québec
U.S. Army Medical Research Acquisition Activity
McGill University
Université de Montréal

The Upjohn Company of Canada
Astra Pharmaceuticals Canada Ltd
Merck Frosst Canada Inc
Fisons Pharmaceuticals Ltd

SCIENTIFIC PROGRAMME

Symposia

Symposia will be held in the "Du Parc I" ballroom. Symposia speakers are requested to personally organize their own slides in the designated carousel at least one hour prior to their presentation. Slides may be previewed in the "Prince Arthur I" room.

Poster Sessions

Posters will be available for on-site discussions with authors from 8:00 - 10:00 a.m. on Monday, Tuesday and Wednesday in the "Du Parc II" ballroom. Authors are requested to attach their material to the appropriate posterboard in the afternoon prior to the morning of the presentation and they should plan on being in attendance for the duration of the scheduled session. **Croissants and coffee will be served during the poster sessions.** Contributors should ensure that their posters are taken down by 1:00 p.m. each afternoon.

Workshops

These informal sessions will be held on Tuesday afternoon and Thursday morning in the following rooms: "Du Parc 2", "Prince Arthur 1", "Prince Arthur 2", "Des Pins 1", "Des Pins 2". Symposium participants who wish to contribute actively to the workshop discussions should bring their slides and other pertinent material to the workshop and they should indicate to the moderators their intention to present data and ideas. The moderators can be contacted during the Symposium through the registration desk.

ADMISSION WILL BE BY REGISTRATION BADGE ONLY

PROGRAMME

SUNDAY, May 12, 1985

12:00 noon - Registration (Foyer)

3:30 p.m. Opening remarks (Du Parc I)

3:45-7.00 p.m. Symposium (Du Parc I)

"STRATEGIES OF GENETIC
ANALYSIS OF HOST
RESISTANCE"

7:00-9:00 p.m. Mixer (Foyer)

Please note: Posters #1-31, scheduled for presentation
at the Monday morning session, will be available for
viewing from Sunday afternoon in the "Du Parc II"
ballroom.

ESKIMO ART EXHIBIT

MONDAY 1 - 3 PM

SALON DES PINS

PROGRAMME

MONDAY, May 13, 1985

8:00 - 10:00 a.m. Poster sessions (Du Parc II)
(with breakfast)

**"GENETIC CONTROL OF RESISTANCE
TO VIRAL INFECTIONS"**
(posters 1-19)

**"HYBRID RESISTANCE AND
SUSCEPTIBILITY TO TUMOR
TRANSPLANTS"**
(posters 20-31)

10:00 - 1:00 p.m. Symposium (Du Parc I)

**"GENETIC CONTROL OF RESISTANCE
TO BACTERIAL INFECTIONS"**

3:00 - 6:00 p.m. Symposium (Du Parc I)

**"GENETIC CONTROL OF RESISTANCE
TO VIRAL INFECTIONS"**

7:00-11:00 p.m. Musical cocktails and dinner,
Restaurant Hélène de Champlain

Buses will leave at 7:00 p.m.
sharp from the main entrance
of Hôtel du Parc

Please note: Posters #32-69, scheduled for presentation
at the Tuesday morning session, will be available for
viewing from Monday afternoon in the "Du Parc II"
ballroom.

PROGRAMME

TUESDAY, May 14, 1985

8:00 - 10:00 a.m. Poster sessions (Du Parc II)
(with breakfast)

"GENETIC CONTROL OF HOST
RESISTANCE TO BACTERIAL
INFECTIONS" (posters 32-64)

"GENETIC CONTROL OF HOST
RESISTANCE TO FUNGAL INFECTIONS"
(posters 65-69)

10:00 - 1:00 p.m. Symposium (Du Parc I)

"GENETIC CONTROL OF RESISTANCE
TO PARASITIC INFECTIONS"

2:30 - 4:30 p.m. Workshops

Herpes viruses (Prince Arthur I)
Trypanosomiasis (Prince Arthur II)
AXB recombinants (Des Pins I)
Macrophage responses (Des Pins II)
Hybrid resistance,
transplantable tumors (Du Parc II)

5:00-7:00 p.m. Workshops

Mycoses (Prince Arthur I)
Salmonellosis,
listeriosis (Prince Arthur II)
Mouse hepatitis viruses (Des Pins I)
Resistance to tumor growth (Des Pins II)
Quantitative genetics (Du Parc II)

Please note: Posters #70-104, scheduled for presentation
at the Wednesday morning session, will be available for
viewing from Tuesday afternoon in the "Du Parc II"
ballroom.

PROGRAMME

WEDNESDAY, May 15, 1985

8:00 - 10:00 a.m. **Poster sessions (Du Parc II)**
(with breakfast)

**"GENETIC CONTROL OF HOST
RESISTANCE TO PARASITIC
INFECTIONS"** (posters 70-90)

**"HOST GENES INFLUENCING
TUMOR GROWTH"** (posters 91-104)

10:00 - 1:00 p.m. **Symposium (Du Parc I)**

**"GENETIC CONTROL OF
SUSCEPTIBILITY TO MALIGNANCY"**

3:00 - 6:00 p.m. **Symposium (Du Parc I)**

**"GENETIC CONTROL OF HOST
RESISTANCE TO MALIGNANCY"**

7:00 p.m. **Banquet (Du Parc II)**

Guest speaker: Dr. Phil Gold
"Leonardo da Vinci is dead."

PROGRAMME

THURSDAY, May 16, 1985

8:30 - 10:00 a.m.

Symposium (Du Parc I)

**"GENETIC CONTROL OF MACROPHAGE
RESPONSES TO INFECTION AND
MALIGNANCY"**

10:30 a.m. - 12:30 p.m. Workshops

Mycobacterial infections (Du Parc I)
Biozzi mice (Prince Arthur I)
Malaria (Prince Arthur II)
NK cells (Des Pins I)
Leishmaniasis (Des Pins II)

DETAILED PROGRAMME

SYMPOSIA (Du Parc I)

(10 minute discussion period will follow each lecture)

Sunday, May 12th 3.30-7.00 p.m.

- 3.30 Opening Remarks - EMIL SKAMENE, Montreal General Hospital Research Institute

STRATEGIES OF GENETIC ANALYSIS OF HOST RESISTANCE

DAVID L. ROSENSTREICH and PHILIPPE GROS, chairing

- 3.45 MICHAEL F.W. FESTING, MRC Laboratory, Animal Center
Strategy in the use of inbred strains in biomedical research
- 4.15 FRANK LILLY, Albert Einstein College of Medicine
Genetic regulation of viral and chemical leukemogenesis
- 4.45 JENFFER M. BLACKWELL, London School of Hygiene & Tropical Medicine
Genetic control of discrete phases of complex infections: Leishmania donovani as a model
- 5.15 Coffee break
- 5.45 GUIDO BIOZZI, Institut Curie
Effect of genetic modification of immune responsiveness in anti-infectious and anti-tumor resistance
- 6.15 DAVID HOUSMAN, Massachusetts Institute of Technology
Strategies of identification and cloning of genomic sequences encoding the genes of host resistance

SYMPOSIA

Monday, May 13, 10.00 a.m. - 1.00 p.m.

GENETIC CONTROL OF RESISTANCE TO BACTERIAL INFECTIONS

EMIL SKAMENE and FRANCINE GERVAIS, chairing

- 10.00 PHILLIP J. BAKER, National Institute of Allergy and Infectious Diseases
Multigenic control of the magnitude of the antibody response to bacterial polysaccharide antigens
- 10.30 IRWIN SCHER, Merck Sharp & Dohme Research Laboratories
Effects of the xid allele on host resistance to infection
- 11.00 JERRY R. MCGHEE, University of Alabama
Lps gene regulation of host immunity and susceptibility to gram negative infections
- 11.25 Coffee break
- 11.45 ALISON D. O'BRIEN, Uniformed Services University of the Health Sciences
Mechanisms of host-gene mediated resistance to murine typhoid: specifics and speculation
- 12.10 DAVID E. BRILES, University of Alabama at Birmingham
Evidence that the pathogenesis of Salmonella typhimurium is dependent on interactions between salmonella and mouse genotypes
- 12.30 ADRIEN M. FORGET, University of Montreal
Genetic regulation of host defense mechanisms controlling mycobacterial infections

SYMPOSIA

Monday, May 13, 3.00-5.30 p.m.

GENETIC CONTROL OF RESISTANCE TO VIRAL INFECTIONS

JEAN-MARIE DUPUY and MARILYN S. SMITH, chairing

3.00 MARGO BRINTON, Wistar Institute of Anatomy and
Biology

**Genetic control of resistance to viral
infections**

3.30 STEPHEN A. STOHLMAN, University of Southern
California

**Genetic control of resistance to mouse
hepatitis virus**

4.00 Coffee break

4.30 OTTO HALLER, University of Zurich

**Mechanisms of genetic resistance to influenza
virus**

5.00 SANDRA RUSCETTI, National Cancer Institute

**Genetic control of resistance to
retrovirus-induced leukemia**

SYMPOSIA

Tuesday, May 14, 10.00 a.m. - 1.00 p.m.

GENETIC CONTROL OF RESISTANCE TO PARASITIC INFECTIONS

ALAN F. SHER and MIKE BELOSEVIC, chairing

10.00 GRAHAM F. MITCHELL, The Walter and Eliza Hall
Institute of Medical Research
**Exploitation of genetically-based variations
in the development of parasite vaccines**

10.30 DONALD L. WASSOM, Cornell University
**Genetic control of the host response to
parasitic helminth infections**

11.00 STEPHANIE L. JAMES, The George Washington
University Medical Center
**Genetic control of resistance to
schistosomiasis**

11.30 Coffee break

12.00 JOHN M. MANSFIELD, University of Wisconsin
**Genetic control of resistance to trypanosomal
infections**

12:30 MARY M. STEVENSON, The Montreal General
Hospital Research Institute
Genetic control of susceptibility to malaria

SYMPOSIA

Wednesday, May 15, 10.00 a.m. - 1.00 p.m.

GENETIC CONTROL OF SUSCEPTIBILITY TO MALIGNANCY

CLIFFORD STANNERS and PAUL JOLICOEUR, chairing

- 10.00 JORGE J. YUNIS, University of Minnesota
Genetics of mutations: chromosomal fragile sites
- 10.30 KATHERINE K. SANFORD, National Cancer Institute
Enhanced G₂ chromosomal radiosensitivity, susceptibility to cancer and neoplastic transformation
- 11.00 DANIEL MERUELO, New York University
Retrovirus integration occurs next to chromosomal sites encoding histocompatibility and lymphocyte differentiation antigens
- 11.30 Coffee break
- 12.00 MICHAEL POTTER, National Cancer Institute
Role of host genes in the susceptibility to plasmacytomas
- 12.30 HERBERT S. MORSE III, National Institute of Allergy and Infectious Diseases
Genes that determine resistance and susceptibility to retrovirus-associated leukemias

SYMPOSIA

Wednesday, May 15, 3.00-6.00 p.m.

GENETIC CONTROL OF HOST RESISTANCE TO MALIGNANCY

GENE M. SHEARER and SUZANNE LEMIEUX, chairing

3.00 RONALD B. HERBERMAN, National Cancer Institute
Role of NK cells in tumor surveillance

3.30 OSIAS STUTMAN, Sloan-Kettering Institute for
Cancer Research
**Possible genetic control of natural cell
mediated cytotoxicity**

4.00 GEORGE A. CARLSON, Jackson Laboratory
**Influences of the major histocompatibility
complex and non-MHC genes on natural resistance
to leukemia cells**

4.30 Coffee break

5.00 ARNOLD GREENBERG, Manitoba Institute of Cell
Biology
**Genetic regulation of natural antitumor
antibody response**

5.30 JOHN RODER, Queen's University
**Mutations affecting natural resistance to
tumors**

SYMPOSIA

Thursday, May 16, 8.30-10.00 a.m.

GENETIC CONTROL OF MACROPHAGE RESPONSE TO INFECTION AND MALIGNANCY

CAROL NACY and DANIEL BOUT, chairing

- 8.30 RICHARD F. MORTENSEN, Ohio State University
Genetic control and induction of the acute
phase reactants
- 9.00 MONTE S. MELTZER, Walter Reed Army Institute
of Research
Genetic control of macrophage activation
- 9.30 DONALD ANDERSON, Baylor College of Medicine
Heritable leukocyte Mac-1, LFA-1, and p150,95
deficiency: Relationship of clinical expression
to functional and molecular abnormalities

WORKSHOPS

Tuesday, May 14, 2.30-4.30 p.m.

1. Genetic variation in macrophage responses to infection. Des Pins II
(Monte Meltzer, moderator).
2. Genetic variation in response to herpesviruses. Prince Arthur I
(G.R. Shellam, moderator).
3. AXB recombinant inbred mouse strains as a tool of genetic analysis of host resistance. Des Pins I
(Muriel Nesbitt, moderator).
4. Models of genetic resistance to infection with trypanosomes. Prince Arthur II
(John Mansfield, moderator).
5. Hybrid resistance and susceptibility to tumor transplants. Du Parc II
(Gene Shearer, moderator).

WORKSHOPS

Tuesday, May 14, 5.00-7.00 p.m.

6. Interpretation and statistical treatment of data derived by segregation analysis and by recombinant inbred strain analysis of quantitative genetic traits. Du Parc II
(David Rosenstreich and R. Dale McCall, moderators).
7. Host genes influencing tumor development. Des Pins II
(Michael Potter, moderator).
8. Mechanisms of genetic resistance to MHV. Des Pins I
(Jean-Marie Dupuy, moderator).
9. Mechanisms of genetic resistance in the models of salmonellosis and listeriosis. Prince Arthur II
(Alison O'Brien and Patricia A.L. Kongshavn, moderators).
10. Genetic control of resistance to fungal infections. Prince Arthur I
(Gabriel Marquis, moderator)

WORKSHOPS

Thursday, May 16, 10.30 a.m. - 12.30 p.m.

- | | |
|---|------------------|
| 11. Models of genetic resistance to mycobacterial infections.
(Emil Skamene, moderator). | Du Parc I |
| 12. H-2 or Hh recognition by natural killer cells - old and novel models testable through advances in molecular genetics?
(Klas Karre, moderator). | Des Pins I |
| 13. Biozzi mice as a model of polygenic regulation of quantitative traits of resistance.
(Guido Biozzi, moderator). | Prince Arthur I |
| 14. Genetic control of cutaneous and visceral leishmaniasis.
(Carol Nacy and Jenefer Blackwell, moderators). | Des Pins II |
| 15. Genetic resistance to malaria.
(Mary M. Stevenson, moderator). | Prince Arthur II |

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REPORT NUMBER #1

SECOND INTERNATIONAL SYMPOSIUM ON GENETIC
CONTROL OF HOST RESISTANCE TO INFECTION
AND MALIGNANCY

FINAL REPORT

Sherwood M. Reichard

November 1, 1985

Supported by

U. S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21701

Contract No. DAMD 17-85-G-5014

Reticuloendothelial Society
Medical College of Georgia
Augusta, GA 30912

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SUMMARY OF SYMPOSIA
GENETIC CONTROL OF HOST RESISTANCE
TO INFECTION AND MALIGNANCY

Montreal, Canada
May 12-16, 1985

The composition of the Organizing Committee, list of sponsors, detailed program and the abstracts may be found in the enclosed program book.

The total registration was 338 participants (including the faculty). The scientific program consisted of 33 keynote lectures (30 minutes each), 104 proffered papers presented as posters and 15 workshops. The Symposium participants commented very positively about the format of poster sessions: These were held daily from 8 - 10 a.m. and croissants and coffee were served near the poster area. This contributed to very leisurely poster discussions with the maximum audience participation. Keynote lectures were of excellent calibre and the informal workshops, moderated by recognized leaders in the specific areas, were generally very lively.

The social program included a buffet dinner with presentation of Quebec folkloric dances and the concluding banquet with a talk by Dr. Phil Gold. Eskimo Art exhibit took place during the Symposium.

The Symposium participants commented very positively on the location of the meeting (Hotel du Parc) and on the scientific and social activities.

Topics discussed at the Symposia included:

PROGRAMME

SUNDAY, May 12, 1985

12:00 noon - Registration (Foyer)
3:30 p.m. Opening remarks (Du Parc I)
3:45-7:00 p.m. Symposium (Du Parc I)
**STRATEGIES OF GENETIC
ANALYSIS OF HOST
RESISTANCE**
7:00-9:00 p.m. Mixer (Foyer)

Please note: Posters #1-31, scheduled for presentation at the Monday morning session, will be available for viewing from Sunday afternoon in the "Du Parc II" ballroom.

ESKIMO ART EXHIBIT
MONDAY 1 - 3 PM
SALON DES PINS

MONDAY, May 13, 1985

8:00 - 10:00 a.m. Post (wit
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Please note: Posters #3 at the Tuesday morning s viewing from Monday afte ballroom.

PROGRAMME

MONDAY, May 13, 1985

8:00 - 10:00 a.m. Poster sessions (Du Parc II)
(with breakfast)

**GENETIC CONTROL OF RESISTANCE
TO VIRAL INFECTIONS**
(posters 1-19)

**HYBRID RESISTANCE AND
SUSCEPTIBILITY TO TUMOR
TRANSPLANTS**
(posters 20-31)

10:00 - 1:00 p.m. Symposium (Du Parc I)

**GENETIC CONTROL OF RESISTANCE
TO BACTERIAL INFECTIONS**

3:00 - 6:00 p.m. Symposium (Du Parc I)

**GENETIC CONTROL OF RESISTANCE
TO VIRAL INFECTIONS**

**7:00-11:00 p.m. Musical cocktails and dinner,
Restaurant Hélène de Champlain**

Buses will leave at 7:00 p.m.
sharp from the main entrance
of Hôtel du Parc

Please note: Posters #32-69, scheduled for presentation
at the Tuesday morning session, will be available for
viewing from Monday afternoon in the "Du Parc II"
ballroom.

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PROGRAMME

TUESDAY, May 14, 1985

8:00 - 10:00 a.m. Poster sessions (Du Parc II)
(with breakfast)

"GENETIC CONTROL OF HOST
RESISTANCE TO BACTERIAL
INFECTIONS" (posters 32-64)

"GENETIC CONTROL OF HOST
RESISTANCE TO FUNGAL INFECTIONS"
(posters 65-69)

10:00 - 1:00 p.m. Symposium (Du Parc I)

"GENETIC CONTROL OF RESISTANCE
TO PARASITIC INFECTIONS"

2:30 - 4:30 p.m. Workshops

Herpes viruses (Prince Arthur I)
Trypanosomiasis (Prince Arthur II)
AXB recombinants (Des Pins I)
Macrophage responses (Des Pins II)
Hybrid resistance,
transplantable tumors (Du Parc II)

5:00-7:00 p.m. Workshops

Mycoses (Prince Arthur I)
Salmonellosis,
listeriosis (Prince Arthur II)
Mouse hepatitis viruses (Des Pins I)
Resistance to tumor growth (Des Pins II)
Quantitative genetics (Du Parc II)

Please note: Posters #70-104, scheduled for presentation
at the Wednesday morning session, will be available for
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ballroom.

WEDNESDAY, May 15, 1985

8:00 - 10:00 a.m. Post
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PROGRAMME

WEDNESDAY, May 15, 1985

Cont'd

8:00 - 10:00 a.m. Poster sessions (Du Parc II)
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"GENETIC CONTROL OF HOST
RESISTANCE TO PARASITIC
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HOST GENES INFLUENCING
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"GENETIC CONTROL OF
SUSCEPTIBILITY TO MALIGNANCY"

3:00 - 6:00 p.m. Symposium (Du Parc I)

"GENETIC CONTROL OF HOST
RESISTANCE TO MALIGNANCY"

7:00 p.m. Banquet (Du Parc II)

Guest speaker: Dr. Phil Gold
"Leonardo da Vinci is dead."

iv

PROGRAMME

THURSDAY, May 10, 1985

8:30 - 10:00 a.m.

CONF Symposium (Du Parc I)

GENETIC CONTROL OF MACROPHAGE
RESPONSES TO INFECTION AND
MALIGNANCY

10:30 a.m. - 12:30 p.m. Workshops

Mycobacterial infections (Du Parc I)
Biozzi mice (Prince Arthur I)
Malaria (Prince Arthur II)
NK cells (Des Pins I)
Leishmaniasis (Des Pins II)

DETAILED PROG

SYMPOSIA (Du P

(10 minute discussion period w

Monday, May 12th 3.30-7.00 p.m.

3.30 Opening Remarks - EMIL SK
Hospital Research Institut

STRATEGIES OF GENETIC ANALYSIS

DAVID L. ROSENSTREICH and PHIL *CONF*

3.45 MICHAEL F.W. FESTING, MRC
Animal Center
Strategy in the use of in
biomedical research

4.15 FRANK LILLY, Albert Einste
Genetic regulation of vir
leukemogenesis

4.45 JENEFER M. BLACKWELL, Lond
Tropical Medicine
Genetic control of discre
infections: Leishmania do

5.15 Coffee break

5.45 GUIDO BIOZZI, Institut Cur
Effect of genetic modifie
responsiveness in anti-in
resistance

6.15 DAVID HOUSMAN, Massachuset
Technology
Strategies of identificat
genomic sequences encodin
resistance

DETAILED PROGRAMME

Cont'd

SYMPOSIA (Du Parc I)

(10 minute discussion period will follow each lecture)

Sunday, May 12th 3.30-7.00 p.m.

3.30 Opening Remarks - EMIL SKAMENE, Montreal General Hospital Research Institute

STRATEGIES OF GENETIC ANALYSIS OF HOST RESISTANCE

DAVID L. ROSENSTREICH and PHILIPPE GROS, chairing

3.45 MICHAEL F.W. FESTING, MRC Laboratory,
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Strategy in the use of inbred strains in
biomedical research

4.15 FRANK LILLY, Albert Einstein College of Medicine
Genetic regulation of viral and chemical
leukemogenesis

4.45 JENNIFER M. BLACKWELL, London School of Hygiene &
Tropical Medicine
Genetic control of discrete phases of complex
infections: Leishmania donovani as a model

5.15 Coffee break

5.45 GUIDO BLOZZI, Institut Curie
Effect of genetic modification of immune
responsiveness in anti-infectious and anti-tumor
resistance

6.15 DAVID ROUSMAN, Massachusetts Institute of
Technology
Strategies of identification and cloning of
genomic sequences encoding the genes of host
resistance

Vi

SYMPOSIA

Monday, May 11, 10.00 a.m. - 1.00 p.m.

GENETIC CONTROL OF RESISTANCE TO BACTERIAL INFECTION

EMIL GRAMMEL and FRANCINE GERVAIS, chairing

10.00 PHILLIP J. BAKER, National Institute of Allergy and Infectious Diseases
Multigenic control of the magnitude of the antibody response to bacterial polysaccharide antigens

10.10 IRWIN SCHER, Merck Sharp & Dohme Research Laboratories
Effects of the xid allele on host resistance to infection

11.00 JERRY R. M. A., University of Alabama
Ips gene regulation of host immunity and susceptibility to gram negative infections

11.10 Coffee break

11.20 ALAN M. M. MORTEN, Uniformed Services University of the Health Sciences
Mechanisms of host-gene mediated resistance to murine typhoid: specifics and speculation

11.30 J. L. BRILES, University of Alabama at Birmingham
Evidence that the pathogenesis of Salmonella typhimurium is dependent on interactions between salmonella and mouse genotypes

11.40 J. M. FORGET, University of Montreal
Genetic regulation of host defense mechanisms controlling mycobacterial infections

SYMPOSIUM

Monday, May 11, 3.00-5.30 p.m.

GENETIC CONTROL OF RESISTANCE

JEAN-MARIE DUPUY and MARILYN

3.00 MARGO BRINTON, Wistar Institute
Biology
Genetic control of resistance to infections

3.30 STEPHEN A. STOHLMAN, University of California
Genetic control of resistance to hepatitis virus

4.00 Coffee break

4.30 OTTO HALLER, University of California
Mechanisms of genetic resistance to virus

5.00 SANDRA RUSCETTI, National Cancer Institute
Genetic control of resistance to retrovirus-induced leukemia

SYMPOSIA

Monday, May 13, 3.00-5.30 p.m.

GENETIC CONTROL OF RESISTANCE TO VIRAL INFECTIONS

LECTIONS

JEAN-MARIE DUPLY and MARILYN S. SMITH, chairing

1.00 MARCO DEBETON, Westar Institute of Anatomy and Biology

Genetic control of resistance to viral infections

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1.30 STEPHEN A. STOHLMAN, University of Southern California

Genetic control of resistance to mouse hepatitis virus

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4.00 Coffee break

4.30 OTTO HALLER, University of Zurich

Mechanisms of genetic resistance to influenza virus

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4.00 SANDRA RUSCETTI, National Cancer Institute

Genetic control of resistance to retrovirus-induced leukemia

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SYMPOSIA

Tuesday, May 14, 10.00 a.m. - 1.00 p.m.

GENETIC CONTROL OF RESISTANCE TO PARASITIC INFECTION

ALAN E. COOPER and MILO BELONJEVIC, Chairing

10.00 GRAHAM F. MITCHELL, The Walter and Eliza Hall
Institute of Medical Research
Exploitation of genetically-based variations
in the development of parasite vaccines

10.30 DONALD L. WASSON, Cornell University
Genetic control of the host response to
parasitic helminth infections

11.00 STEPHANIE L. JAMES, The George Washington
University Medical Center
Genetic control of resistance to
schistosomiasis

11.30 Coffee break

12.00 JOHN M. MANSFIELD, University of Wisconsin
Genetic control of resistance to trypanosomal
infections

12.30 NANCY M. SILVERSON, The Montreal General
Hospital Research Institute
Genetic control of susceptibility to malaria

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SYMPOSIA

Wednesday, May 15, 10.00 a.m. -

GENETIC CONTROL OF SUSCEPTIBILITY

CLIFFORD STANNERS and PAUL JOHNSON

10.00 JORGE J. YUNIS, University of Maryland
Genetics of mutations: sites

10.30 KATHERINE K. SANFORD, M.D.
Institute
Enhanced G₂ chromosomal
susceptibility to cancer
transformation

11.00 DANIEL MERUELO, New York University
Retrovirus integration
chromosomal sites encoding
and lymphocyte differentiation

11.30 Coffee break

12.00 MICHAEL POTTER, National Cancer Institute
Role of host genes in the development of
plasmacytomas

12.30 HERBERT S. MORSE III, National Cancer Institute
Allergy and Infectious Diseases
Genes that determine resistance
susceptibility to retroviral
leukemias

SYMPOSIA

Wednesday, May 15, 10.00 a.m. - 1.00 p.m.

GENETIC CONTROL OF SUSCEPTIBILITY TO MALIGNANCY

INFECTIONS

CLIFFORD STANNERS and PAUL JOLICOEUR, chairing

2nd Hall

10.00 JORGE J. YUNIS, University of Minnesota
Genetics of mutations: chromosomal fragile sites

lations

10.30 KATHERINE K. SANFORD, National Cancer Institute
Enhanced G₂ chromosomal radiosensitivity, susceptibility to cancer and neoplastic transformation

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11.00 DANIEL MERUELO, New York University
Retrovirus integration occurs next to chromosomal sites encoding histocompatibility and lymphocyte differentiation antigens

11.30 Coffee break

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12.00 MICHAEL POTTER, National Cancer Institute
Role of host genes in the susceptibility to plasmacytomas

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alaria

12.30 HERBERT S. MORSE III, National Institute of Allergy and Infectious Diseases
Genes that determine resistance and susceptibility to retrovirus-associated leukemias

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SYMPOSIA

Wednesday, May 15, 3.00-6.00 p.m.

GENETIC CONTROL OF HOST RESISTANCE TO MALIGNANCY

GENE M. SHEARER and SUZANNE LEMIEUX, chairing

3.00 RONALD B. HERBERMAN, National Cancer Institute
Role of NK cells in tumor surveillance

3.30 OSLAS STUTMAN, Sloan-Kettering Institute for
Cancer Research
Possible genetic control of natural cell
mediated cytotoxicity

4.00 GEORGE A. CARLSON, Jackson Laboratory
Influences of the major histocompatibility
complex and non-MHC genes on natural resistance
to leukemia cells

4.30 Coffee break

5.00 ARNOLD GREENBERG, Manitoba Institute of Cell
Biology
Genetic regulation of natural antitumor
antibody response

5.30 JOEL RUDER, Queen's University
Mutations affecting natural resistance to
tumors

SYMPOSIA

Thursday, May 16, 8.30-10.00 a.m.

GENETIC CONTROL OF MACROPHAGE AND MALIGNANCY

CAROL NACY and DANIEL BOUT, chairing

8.30 RICHARD F. MORTENSEN, OH
Genetic control and indu-
phase reactants

9.00 MONTE S. MELTZER, Walter
of Research
Genetic control of macro

9.30 DONALD ANDERSON, Baylor
Heritable leukocyte Mac-
deficiency: Relationship
to functional and molecu

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SYMPOSIA

Thursday, May 16, 8.30-10.00 a.m.

**GENETIC CONTROL OF MACROPHAGE RESPONSE TO INFECTION
AND MALIGNANCY**

CAROL NACY and DANIEL BOUT, chairing

**8.30 RICHARD F. MORTENSEN, Ohio State University
Genetic control and induction of the acute
phase reactants**

**9.00 MONTE S. MELTZER, Walter Reed Army Institute
of Research
Genetic control of macrophage activation**

**9.30 DONALD ANDERSON, Baylor College of Medicine
Heritable leukocyte Mac-1, LFA-1, and p150,95
deficiency: Relationship of clinical expression
to functional and molecular abnormalities**

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WORKSHOPS

Tuesday, May 14, 2.30-4.30 p.m.

1. Genetic variation in macrophage responses to infection.
(Monte Meltzer, moderator).
2. Genetic variation in response to herpesviruses.
(G.R. Shellam, moderator).
3. AXB recombinant inbred mouse strains as a tool of genetic analysis of host resistance.
(Charles Neuhill, moderator).
4. Models of genetic resistance to infection with trypanosomes.
(John Mansfield, moderator).
5. Hybrid resistance and susceptibility to tumor transplants.
(Gene Shearer, moderator).

Des Pins II

Prince Arthur

Des Pins I

Prince Arthur I

Du Parc II

WORKSHOPS

Tuesday, May 14, 5.00-7.00 p.m.

6. Interpretation and statistics of data derived by segregation and by recombinant inbred str of quantitative genetic trait
(David Rosenstreich and R. Da moderators).
7. Host genes influencing tumor development.
(Michael Potter, moderator).
8. Mechanisms of genetic resistance to HIV.
(Jean-Marie Dupuy, moderator).
9. Mechanisms of genetic resistance in the models of salmonellosis and listeriosis.
(Alison O'Brien and Patricia A.L. Kongshavn, moderators).
10. Genetic control of resistance to fungal infections.
(Gabriel Marquis, moderator).

WORKSHOPS

Tuesday, May 14, 5.00-7.00 p.m.

6. Interpretation and statistical treatment of data derived by segregation analysis and by recombinant inbred strain analysis of quantitative genetic traits. (David Rosenstreich and R. Dale McCall, moderators). Du Parc II
Pins II e Arthur I
7. Host genes influencing tumor development. (Michael Potter, moderator). Des Pins II
Pins I
8. Mechanisms of genetic resistance to HIV. (Jean Marie Dupuy, moderator). Des Pins I
Arthur II
9. Mechanisms of genetic resistance in the models of salmonellosis and listeriosis. (Alison O'Brien and Patricia A.L. Kongshavn, moderators). Prince Arthur II
rc II
10. Genetic control of resistance to fungal infections. (Gabriel Marquis, moderator) Prince Arthur I

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WORKSHOPS

Thursday, May 16, 10.30 a.m. - 12.30 p.m.

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| 11. Models of genetic resistance to mycobacterial infections.
(Emil Skamene, moderator). | Du Parc I |
| 12. H-2 or Hh recognition by natural killer cells - old and novel models testable through advances in molecular genetics?
(Klas Karre, moderator). | Des Pins I |
| 13. Blozzi mice as a model of polygenic regulation of quantitative traits of resistance.
(Guilio Blozzi, moderator). | Prince Arthur I |
| 14. Genetic control of cutaneous and visceral leishmaniasis.
(Carol Nacy and Jenefer Blackwell, moderators). | Des Pins II |
| 15. Genetic resistance to malaria.
(Mary M. Stevenson, moderator). | Prince Arthur II |

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II. INTERNATIONAL SYMPOSIUM ON
**GENETIC CONTROL OF
HOST RESISTANCE TO
INFECTION
AND MALIGNANCY** RES

**WORKING PAPER
DO NOT PHOTOGRAPH**

08 JAN 1986



Montreal, Canada
May 12-16, 1985

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SUMMARY OF SYMPOSIA
GENETIC CONTROL OF HOST RESISTANCE
TO INFECTION AND MALIGNANCY

Montreal, Canada
May 12-16, 1985

The composition of the Organizing Committee, list of sponsors, detailed program and the abstracts may be found in the enclosed program book.

The total registration was 338 participants (including the faculty). The scientific program consisted of 33 keynote lectures (30 minutes each), 104 proffered papers presented as posters and 15 workshops. The Symposium participants commented very positively about the format of poster sessions: These were held daily from 8 - 10 a.m. and croissants and coffee were served near the poster area. This contributed to very leisurely poster discussions with the maximum audience participation. Keynote lectures were of excellent calibre and the informal workshops, moderated by recognized leaders in the specific areas, were generally very lively.

The social program included a buffet dinner with presentation of Quebec folkloric dances and the concluding banquet with a talk by Dr. Phil Gold. Eskimo Art exhibit took place during the Symposium.

The Symposium participants commented very positively on the location of the meeting (Hotel du Parc) and on the scientific and social activities.

RESISTANCE OF INBRED MICE TO HERPES SIMPLEX VIRUS (HSV) INFECTION IS GOVERNED BY LOCI ON CHROMOSOMES 4 AND 14. Maria C. Savoia, Muriel N. Nesbitt, Theo N. Kirkland, Douglas D. Richman and Michael N. Oxman, VAMC & UCSD, San Diego, CA 92161

Inbred mice vary greatly in their susceptibility to HSV infection. Although the mechanism of inherited resistance is not clearly established, resistance is dominant and appears to be immunologically mediated. Backcross analyses have suggested that two major, independently segregating, non H-2 loci may be involved. We have examined the susceptibility to HSV-1 infection of 39 recombinant inbred (RI) strains derived from sensitive ($LD_{50}=10^{2.5}$ pfu) A/J and resistant ($LD_{50}>10^6$ pfu) C57BL/6 parents. RI and parental strains were infected intraperitoneally with 10^4 pfu of HSV-1 and mortality was observed over 21 days. Susceptibility and resistance were determined by the Fisher Exact test, comparing the observed mortalities to those of simultaneously infected parental controls. A locus governing resistance was found to be linked to the brown (b) locus on chromosome 4. Only 1 of the 16 strains tested that are C57BL/6-like at the (b) locus was susceptible. In addition, the presence of a second locus was suggested by the observation that approximately half of the RI strains that are A/J-like at the (b) locus were, nevertheless, resistant to HSV-1. This second locus appears to be linked to erythrocyte nucleoside phosphorylase activity (NP-2) on chromosome 14. In general, resistant strains that are A/J-like at (b) have C57BL/6 NP-2 activity, whereas susceptible strains that are A/J-like at (b) have A/J NP-2 activity. (Incidence of recombination = 3/18 strains, yielding a map distance of 6 cM with a 95% confidence interval of 3 cM to 12 cM.) These data indicate that 2 different loci govern resistance to intraperitoneal infection with HSV-1. One is closely linked to the (b) locus on chromosome 4 and the other is on chromosome 14. Mice are resistant when either locus from the resistant parent is present.

SYNERGISTIC EFFECTS OF MURINE CYTOMEGALOVIRUS (MCMV) AND GRAFT VERSUS HOST (GVH) INDUCED IMMUNE SUPPRESSION. C.S. Via, Natl. Cancer Inst., Bethesda, MD 20205, J.D. Shanley, Univ. Conn., Newington, CT, J.E. Grundy, Royal Free Hosp. London, Eng, G.M. Shearer, Bethesda, MD.

A relationship between MCMV infection and the induction of GVH induced immune deficiency was studied using the parent into F_1 model. 20×10^6 , 10×10^6 or 2×10^6 parental spleen cells from B10.A mice were injected intravenously into (C57Bl/10xB10.A) F_1 mice. CMV infection was accomplished using 1 LD₅₀ (for adult BALB/c female mice) intraperitoneally (IP) to either the parental donor or the F_1 host at various times prior to donor spleen cell transfer. Uninfected controls received normal salivary gland suspensions IP 14 days after spleen cell transfer, immune function was assessed as the ability to generate in vitro cytotoxic lymphocyte responses to modified self or alloantigens. Prior infection of the F_1 host with MCMV resulted in a lower threshold cell number for the induction of GVH related immune deficiency. Conversely, larger inocula of cells were required to induce suppression when donor mice received prior MCMV infection. Thus, prior MCMV infection of the host appears more critical than that of the donor in determining susceptibility to GVH in this model. This effect is most pronounced when cell transfer occurs early post infection (3 days) but is still apparent as long as 10 days post infection. These findings may have relevance to the frequent association of CMV infection and chronic GVH reaction in bone marrow transplant patients.

THE ROLE OF INTERFERON IN THE EXPRESSION OF GENETICALLY
DETERMINED RESISTANCE TO MURINE CYTOMEGALOVIRUS (MCMV).

G.B. Harnett and G.R. Shellam*, Virology Laboratory,
State Health Laboratory Services, QEII Medical Centre,
Nedlands, and* Department of Microbiology, University
of Western Australia, Nedlands, Western Australia.

In mice resistance to fatal MCMV-infection is controlled by H-2 associated genes, the H-2^k haplotype being protective, and by non-H-2 genes. The resistant phenotype is manifest in adult mice, newborns and in vitro in embryo fibroblasts (MEF) from resistant strains. Although the resistance mechanisms are not fully understood, interferon (IFN) plays an important role. IFN α /R is more effective in genetically resistant strains, although this is not due to greater production of IFN but to a greater sensitivity to IFN in resistant mice. Thus in MEF exposed to 500u/ml of IFN α , and the same dose of MCMV, plaque numbers were reduced by 30% in susceptible BALB/c and BALB.B cells, 42% in BALB.K, 45% in C3H, 48% in CBA and 64% in B10.BR cells, this pattern of increasing sensitivity to IFN matching the increasing resistance status of these strains. Greater reductions were still seen in MEF from resistant strains even when these cells received a higher virus dose. These strain variations in the effects of IFN were also seen in mice which received four daily doses of 3000 units of IFN α beginning on the day of birth with a lethal challenge (8×10^2 pfu) of CMV on day 2. BALB/c and C57BL/6 mice were not protected while in CBA and C3H survival was prolonged and 40%, and 60% respectively were completely protected. IFN α protected resistant CBA mice even when the dose of MCMV was increased although protection was lost at high doses. However, when HSV-1 was used, IFN α protected the genetically resistant C57BL/6 strain but not susceptible CBA or BALB/c mice. This virus-specific effect of IFN α for MCMV or HSV-1 is reminiscent of the effect of the Mx gene on influenza virus, and suggests that in vivo, resistance to MCMV or HSV-1 may result from interactions between endogenous IFN and the resistance genes of the host.

GENETIC BACKGROUND MODULATES THE EFFECTS OF THE BEIGE AND NUDE MUTATIONS ON SUSCEPTIBILITY TO MCMV.

G.R. Shellam, J.P. Flexman, H.E. Farrell & J.M. Papadimitriou*, Depts. of Microbiology & Pathology*, University of Western Australia, Nedlands, Western Australia.

In mice genetically determined resistance to murine cytomegalovirus (MCMV) is manifest early in the course of the infection, and NK cells and IFN have been implicated as important mediators of resistance. We previously reported that C57BL/6 bg/bg were more susceptible to MCMV than C57BL/6 bg/+. However, when the effect of the gene was compared in four strains of mice of differing resistance status, the increase in susceptibility varied depending on the mouse strain. C57BL/6, SB/Le, DBA/2 and CBA bg/bg showed respectively a 2.5, 3.2, 9.5 and 18.6 fold increase in susceptibility compared with bg/+. Of these strains CBA are the most genetically resistant and the extent of the reduction in resistance by the bg gene in CBA mice is noteworthy because the difference in LD₅₀ between the most resistant and susceptible strains is only 30-40 fold. Beige mice exhibited higher liver titres of MCMV by days 2-3 after infection and died sooner, and tissue damage was greater than in bg/+ mice. Endogenous NK cell activity was markedly depressed in bg/bg compared to bg/+ and following MCMV infection, the increment in cytotoxicity was much greater in bg/+. However neither cytotoxicity towards WEHI-164 cells nor the production of IFN was impaired by the beige mutation. The nude gene also increased susceptibility to MCMV as judged by virus titres, but in contrast to the bg gene its effect was greater in genetically susceptible strains such as BALB/c than in resistant CBA mice. However virus titres were lower in nu/nu than nu/+ over the first 5-7 days of the infection and nu/nu died later than nu/+. The major effect of the bg mutation in the genetically resistant CBA strain and the contrasting effects of the nude mutation in this strain suggest that NK cells rather than T cells are important early in the infection in genetically resistant mice.

GENETIC RESISTANCE TO MURINE CYTOMEGALOVIRUS (MCMV) AND
HSV-1 IN NEWBORN MICE

G.R. Shellam & J.P. Flexman, Department of Microbiology,
University of Western Australia, Nedlands 6009,
Western Australia.

The effectiveness of genetically controlled mechanisms of resistance to virus infections has not been widely studied in newborn animals, although the greater susceptibility of newborn compared with adult animals has been well documented. Since we have previously observed genetically determined resistance to MCMV and HSV-1 in vitro in mouse embryo fibroblasts, we have investigated whether resistance genes influence MCMV or HSV-1 infection in newborn mice. Mice of a number of strains were infected i.p. on the day of birth with one of a number of doses of MCMV or HSV-1 using at least 3 litters per dose. As expected, newborn mice were much more susceptible than adults although there were strain dependent variations in the development of lethal disease which were virus specific and resembled those seen in adult mice. Thus MCMV resistance in the H-2^K haplotype was protective (B10.BR and BALB.K were significantly more resistant than C57BL/10 or BALB/c respectively), as well as non-H-2 genes in C57BL mice. Resistance to HSV-1 was independently regulated and non-H-2 genes in C57BL/6 were protective. Resistance was also reflected in the organ titres of these viruses. MCMV titres in the spleen or liver were at least 100 fold lower in B10.BR and CBA than in BALB/c by days 3 to 4, and similarly the titre of HSV-1 was 65 fold lower in B10.A than A/J. For MCMV but not HSV-1 survival time was significantly longer for resistant strains, even with high lethal doses of virus. Fostering experiments showed that resistance was not influenced by the genetic resistance status of the mother. This raises the intriguing possibility that such virus specific mechanisms may exist in newborns of many species including man, and may provide protection prior to the development of the immune system.

GENETICS OF INNATE RESISTANCE TO ECTROMELIA VIRUS (MOUSEPOX) IN INBRED STRAINS OF MICE. R. Mark L. Buller, G.D. Wallace and H.C. Morse III. Laboratory of Viral Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20205.

Ectromelia virus, a member of the orthopoxvirus genus, is a natural pathogen of mice, causing a lethal disease in some strains of mice but not others. The mechanisms responsible for this difference in mouse strain susceptibility to disease are poorly understood, but a genetic contribution has been clearly established. Crosses of the resistant strain C57BL/6J(B6, with susceptible BALB/c(C), DBA/2 (D2) or A/J (A) mice yielded F_1 progeny which were resistant to ectromelia virus-induced mortality. This indicated that resistance was a dominant characteristic in B6 mice, and recessive in A, BALB/c and DBA/2. The LD_{50} for (B6xA) F_1 mice was similar to that of B6 alone which suggested that the resistance gene is not co-dominant. When resistant F_1 females and susceptible males of the strains A, BALB/c and DBA/2 were bred, the resistance trait behaved as a single autosomal dominant gene in the (B6xA) F_1 xA cross, and as two or more independently assorting loci in the (B6xC) F_1 xC and (B6xD2) F_1 xD2 crosses. There also appeared to be differences in resistance to mousepox between males and females of the same cross. Studies utilizing castrated male and female mice have indicated that at least a portion of this sex-related resistance is explained by hormonal influences.

MHC-CONTROLLED RESISTANCE TO A HERPESVIRUS-INDUCED TRANSIENT PARALYSIS IN CHICKENS: ASSOCIATION WITH LOW ANTIBODY RESPONSE TO THE VIRUS. Louis Schierman and Kent Tseng, Department of Avian Medicine, University of Georgia, Athens, GA 30605

Marek's disease virus (MDV) is an oncogenic herpesvirus of chickens that can cause a neurological disorder, called transient paralysis (TP), in a small proportion of infected outbred chickens. Symptoms of TP generally occur between 9 and 11 days post-MDV infection and range from mild ataxia to total body paralysis. Most affected birds recover in 24 to 48 hours although severely paralyzed birds usually die during the same time period. From earlier studies with two related inbred lines of chickens, along with F_1 and backcross offspring, we found TP resistance to be expressed as a dominant trait controlled by MHC genes. Line G-B1 birds (MHC genotype B^{13}/B^{13}) are TP-resistant while line G-B2 birds (MHC genotype B^6/B^6) are highly susceptible. Other previous investigations in this laboratory showed that TP is a central nervous system (CNS) disorder, characterized by lesions indicative of vasogenic brain edema, and that the disease can be prevented by humoral immunosuppression (neonatal bursectomy or cyclophosphamide treatment). We now report findings that indicate TP resistance is not completely dominant because some MDV-inoculated F_1 and heterozygous B^6/B^{13} F_2 birds have displayed mild symptoms of the disease. Tests with 7 strains of MDV revealed large variations in severity and incidence of symptoms induced by different strains. In addition, studies with G-B1, G-B2 and F_2 generation birds show that early production of anti-MDV precipitating antibodies is controlled by MHC genes. Most B^6/B^6 and B^6/B^{13} birds produce the antibodies, detectable by agar gel diffusion, at a time when most B^{13}/B^{13} birds do not. The differences observed in anti-MDV antibody production, along with the previous immunosuppression results, support the hypothesis that TP is an immune complex or autoimmune disorder mediated by antibodies. This model may prove useful for investigating mechanisms that underlie human CNS disorders thought to have a viral etiology. (Supported by NIH grant NS 16770.)

NON H-2 RELATED RESISTANCE GENES TO MHV3 INFECTION EXPRESSED IN LYMPHOID CELLS AND MACROPHAGES. Lucie Lamontagne and Jean-Marie Dupuy, Département des Sciences Biologiques, UQAM and Centre de recherche en immunologie, Institut Armand-Frappier, Université du Québec, Laval.

Mouse hepatitis virus 3 (MHV₃) infection displays various types of sensitivity according to mouse strains. Persistent MHV₃ infection can readily be induced in vitro in fibroblast or lymphocyte cultures. Disappearance of in vivo pathogenicity occurred however when wild virus was replicated in lymphoid cell lines (e.g. YAC cells). In order to characterize the mechanisms responsible for MHV₃ genetically-determined in vivo pathogenicity, virus replication was studied in cells obtained from various target organs, using pathogenic L2-MHV₃ and non-pathogenic YAC-MHV₃. Cells originated from various mouse strains exhibiting different sensitivities. Results indicated that no significant differences between mouse strains were observed in virus production in brain, liver, spleen and lymph nodes during the first 3 days after infection. No virus, however, was detected in thymus after infection with YAC-MHV₃. In vitro permissivity of peritoneal exudate cells, nonadherent spleen cells and thymocytes was different for L2-MHV₃ and for YAC-MHV₃. Results observed in semisusceptible congenic mouse strains indicated that resistance to in vitro permissivity was not H-2 linked. These results strongly suggest that in vivo pathogenicity of MHV₃ is associated with the permissivity for virus replication in macrophages and lymphoid cells.

(Supported by MRC).

CLASS I MHC GENES AND MURINE HEPATITIS TYPE 3(MHV3)-INDUCED PARALYSIS. Daniel Oth, Vera Cainelli-Gebara, Drasko Pekovic and Jean-Marie Dupuy. Institut Armand-Frappier, Laval-des-Rapides, Quebec, H7N 4Z3.

Susceptibility to MHV3-induced paralysis is governed by at least 3 different genes, including H 2. The H-2^f and H2^q haplotypes, contrarily to a number of others, confer a dominant protection against paralysis. Using F₁ hybrids made with the A/J strain and with various H-2-recombinant strains, bearing H-2^f or H-2^q alleles at different loci of the H-2 complex, we observed that heterozygotes bearing either H-2K^q or H2D^f exhibited significantly less paralysees than non-H-2^q or non-H-2^f controls. They were, however, less protected than controls bearing the H-2^f or H-2^q haplotypes. These results indicate that genes closely associated with H-2K and H-2D are able to exert an efficient but partial protection against paralysis, and suggest a role for class I genes or gene products in the control of paralysis. Expression of class I antigens in brain lesions is currently being studied, using a direct immunofluorescence technique, since recent findings demonstrated that substances associated with interferon were able to induce such an expression on brain cells.

Supported by the Medical Research Council of Canada, (MA7241) and the MS Society of Canada.

SUSCEPTIBILITY/RESISTANCE TO MURINE HEPATITIS VIRUS STRAIN 3 (MHV-3) AND MONOCYTE PROCOAGULANT ACTIVITY (MPCA) ARE GENETICALLY LINKED AND CONTROLLED BY 2 NON H-2 LINKED GENES. Vincents Dindzans, Emil Skamene and Gary Levy, University of Toronto and Montreal General Hospital.

Resistance or susceptibility to MHV-3 infection in inbred mice shows genetic variation. The mode of inheritance of this trait was determined by typing the set of AXB/BXA recombinant inbred (RI) strains derived from resistant A/J (A) and susceptible C57Bl/6J (B) progenitors for susceptibility to infection as determined by the severity of liver disease, viral replication and survival. The strain distribution pattern (SDP) of susceptibility showed a discontinuous variation: 2 strains were fully resistant (A-like), 5 were fully susceptible (B-like) and 15 strains showed an intermediate degree of susceptibility. This SDP best fits the two gene model of inheritance with neither of these two loci linked to the H-2 gene complex. The MPCA which was previously demonstrated to correlate with the disease susceptibility likewise segregated among the RI strains in an SDP identical to that of resistance/susceptibility. MPCA was 25 ± 5 mU/ 10^5 splenic macrophages for resistant strains, 145 ± 20 mU for semisusceptible strains and 2150 ± 100 mU/ 10^6 splenic macrophages in the fully susceptible mice. These observations constitute a proof of genetic linkage (or identity) of chromosomal loci controlling the susceptibility to disease and MPCA. The mapping of the genes controlling these traits, using an expanded set of AXB/BXA RI strains will permit us to: (1) type the susceptible and resistant individuals in the population and (2) analyse the mechanisms of genetic resistance at the molecular level. Supported by the Medical Research Council of Canada.

GENETIC CONTROL OF DELAYED-TYPE HYPERSENSITIVITY
IN MICE INFECTED WITH MOUSE HEPATITIS VIRUS.

Shigeru Kyuwa, Kenjiro Yamaguchi, Kosaku Fujiwara
and Kazuya Yamanouchi, Institute of Medical
Science, University of Tokyo, Tokyo 108, Japan.

Delayed-type hypersensitivity (DTH) in mouse hepatitis virus (MHV) infection was studied using 13 inbred and congenic strains of mice. SWR/J and H-2 congenic mice with C57BL/10 background were shown to be higher responders while A/J, BALB/c, C3H/He, C57BL/6, C58/J, CBA/J, DBA/2 and SJL/J lower responders. The response was not correlated with coat color genes, sex, H-2, immunoglobulin allotype nor with susceptibility to intracerebral infection with MHV. Genetic analysis indicated that low DTH responsiveness to MHV was inherited as a dominant trait with probably polygenic control. Radiation chimeras of the high responder B10.D2 and low responder DBA/2 mice expressed the same responses as the bone marrow donors. Cyclophosphamide treatment and cell transfer experiments between these two mice suggested no difference in the effector T cell activity between the two and no suppressor T cells involved in the response of the low responder. Of MHV-infected mice the strain difference was observed also in DTH response to SRBC, suggesting that the strain difference in DTH responsiveness during MHV infection might be due to difference in response of bone marrow-derived mononuclear cells to lymphokines.

PESTICIDE-INDUCED SUPPRESSION OF NATURAL RESISTANCE TO MOUSE HEPATITIS VIRUS 3. Krzysztof Krzystyniak, Jacques Bernier, Patrice Hugo and Michel Fournier, Department of Biological Sciences, Université du Québec à Montréal, Montreal, P.Q. H3C 3P8

Interaction of selected pesticides, organochlorine, organophosphate and carbamate, with genetically-controlled, early resistance to mouse hepatitis virus 3 (MHV3) was examined in susceptible C57B1/6 and semisusceptible (C57B1/6 x A/J) F_1 mouse strains. In vivo experiments showed increased¹ susceptibility to acute MHV3-disease of animals exposed to single, subacute doses of selected pesticides. In vitro studies of cellular and functional macrophage parameters showed: (i) the cellular parameters like viability, adherence to plastic, superoxide anion production by oil-elicited and virus-activated macrophages were not inhibited by previous exposure to subacute doses of pesticides; (ii) virus-macrophage interaction, such as adsorption and uptake of ³H-labelled MHV3, replication and production of infectious MHV3 particles were not altered by pesticide exposure; (iii) virus-induced cytolysis, however, was significantly increased in macrophages originating from animals exposed previously to dieldrin, carbofuran, Guthion, sevin and matacil. This was determined by quantification of MHV3-induced, cytolysis-specific ⁵¹Cr-release from virus-infected macrophages originating from animals exposed previously to the pesticide.

In conclusion, exposure to pesticides can increase susceptibility to acute MHV3-disease, possibly by inhibiting the natural resistance of the host. The primary target cells for MHV3 infection, peritoneal macrophages expressed increased susceptibility to virus-induced cytolysis. Significantly increased mortality in semisusceptible (C57B1/6 x A/J) F_1 hybrids indicated the possible alteration by pesticides of the expression of genetic factor(s) of natural antiviral resistance.

(Supported by NSERC)

PICHINDE VIRUS INFECTION AND DIFFERENCES IN LYMPHOCYTE RESPONSIVENESS TO LYMPHOKINES IN TWO INBRED STRAINS OF SYRIAN HAMSTER. Kathryn E. Wright, David A. Clark and William E. Rawls. Dept. of Pathology, McMaster University, Hamilton, Canada, L8N 3Z5.

Two inbred strains of Syrian hamster have been shown to display genetically determined differences in resistance to Pichinde virus (PV) infection. After intraperitoneal injection, the virus grows to higher titres in the spleens of the susceptible strain, MHA, than in the spleens of the resistant strain, LSH. It was noted that MHA hamsters show higher natural killer cell (NK) activity both endogenously and after PV infection than LSH hamsters. Further experiments were carried out to examine the relationship of higher NK activity to the course of viral infection. First, the spleens and thymi of MHA hamsters display greater cellularity than those of LSH animals. Second, thymocytes from MHA hamsters proliferate to a greater extent than those from the other strain in response to Concanavalin A-induced conditioned medium (CM) or Interleukin 2 (Il-2) plus mitogen. Splenocytes from the MHA strain also show high levels of lymphokine activated killer cell (LAK) activity after culture in CM or Il-2, in contrast to LSH splenocytes, and this difference is attributable to a greater frequency of LAK precursors in the spleens of MHA than LSH hamsters. These observations have led to the hypothesis that the precursor cells in MHA spleens are the cells expressing endogenous NK activity, and may serve as target cells for virus replication early in the pathogenesis of Pichinde infection.

(This work was supported by grants from the National Cancer Institute of Canada and the Medical Research Council)

VARIATION IN SEVERITY OF COXSACKIEVIRUS B₃-INDUCED MYOCARDITIS AMONG H-2 CONGENIC MOUSE STRAINS. Kirk W. Beisel, LuAnne J. Wolfgram, Monica Traystman, Noel R. Rose and Ahvie Herskowitz, Departments of Immunology & Infectious Diseases and Medicine, The Johns Hopkins Medical Institutes, Baltimore, MD. 21205.

A large panel of H-2 congenic mouse strains were examined for their susceptibility to CB₃-induced myocarditis. This panel consisted of 4 A, 12 B10, 4 C3H and 3 BALB H-2 congenic lines. Two week old animals from each strain were infected with 10⁵ TCID₅₀ of CB₃ (Nancy). Animals were killed at days 5, 7 and 10 after infection and various tissue samples were collected. Two patterns of histopathologic changes were seen in the heart of the various mouse strains examined. The first pattern is the more typical collection of fibrocalcific foci randomly distributed throughout the left and right ventricles. The lesions are composed of loose, organized connective tissue with a cellular infiltrate composed primarily of mononuclear cells and occasional clusters of polymorphs. Although the lesions are fairly well circumscribed, the periphery of the lesions have finger-like extensions projecting into the adjacent myocardium. The overall pattern, though, is that of multifocal fibrocalcific lesions. In addition, the most affected cases contain a sparse interstitial mononuclear infiltrate which surround normal appearing myocytes. This pattern is shared by the following strains: B10.Q, C3H.NB, C3H.JK, C3H.SW, A/J, A.SW, A.BY and A.CA. The other pattern was observed in BALB.K, B10.BR, B10.SM, B10.M, B10.D2, B10.S and B10.PL animals and is typified by fibrous scars which consist of inflammatory cells within linear bands of fibrous connective tissue rather than discrete foci of necrosis. These linear bands of connective tissue contain the same degree of mononuclear cell infiltrate as in the first pattern and, in addition, the interstitial mononuclear cell response appears to be similar. Furthermore, quantitative differences in severity of myocarditis was observed among the H-2 congenic strains. These data demonstrate that both MHC and non-MHC genes influence the severity of CB₃-induced myocarditis. (This work was supported by PHS grants HL-27932, HL-30144 and CA-34202.)

A NOVEL NEURO-IMMUNOLOGICAL ILLNESS AMONG CREE INDIAN CHILDREN. D. Black,* C.M. Tsoukas,* G.V. Watters,† E. Reece,† C. Dumont,* P. Gold,* J. Hoey.* Montreal General Hospital,* Montreal and Montreal Children's Hospital,† Montreal.

Nine closely related Cree Indian children in an isolated and highly inbred community in Northern Quebec suffered from an unusual and fatal neurological illness. The neurological illness consisted of severe mental retardation, microcephaly, blindness, spasticity and athetoid movements. At autopsy brain histology showed cerebral atrophy, widespread patchy demyelination, cerebral calcifications, and perivascular inflammation. Immunoperoxidase staining of vessel endothelium was positive for IgG and IgM. Affected children also had clinical and immune abnormalities similar to those described in the AIDS-related complex (ARC), namely: peripheral lymphadenopathy, splenomegaly, polyclonal hypergammaglobulinemia, circulating immune complexes, and low T helper: suppressor ratios. Most had evidence of CMV or EBV infection. Ninety other Cree individuals, including families of the affected children, had no immune abnormalities. It is proposed that this novel neuro-immunological disease represents an inherited defect in cell mediated immunity with atypical central nervous system infection. The relationship, if any, of this illness to a retroviral agent remains to be determined.

POLYGENIC CONTROL OF VIRAL ANTIGEN EXPRESSION AND INDUCTION OF ANTI-AKR/GROSS VIRUS CTL BY H-2, FV-1, AND VIRAL GENES: GENE DOSAGE EFFECTS. William R. Green, Dartmouth Medical School, Hanover, NH. 03756.

Previously, we raised H-2K^b restricted C57BL/6 cytolytic T lymphocytes vigorously lytic for tumor cells induced by endogenous AKR/Gross leukemia viruses. H-2 encoded gene control was involved in the generation of antiviral CTL. Responder H-2^b, as opposed to non-responder H-2^k, genes were necessary but not sufficient for antiviral CTL production because AKR.H-2^b mice were non-responders. In contrast in the present study, "doubly congenic" AKR.H-2^b:Fv-1^b mice were found to respond, though not as vigorously as B6 mice. Fv-1ⁿ thus appeared to exert negative epistatic control over positive H-2^b effects. Fv-1 mediated control depended on additional gene(s) of the AKR background since B6.Fv-1ⁿ congenics responded fully. A likely mechanism for Fv-1ⁿ mediated negative control appeared to be its permissiveness in allowing the expression of endogenous N-ecotropic leukemia virus associated antigens with ensuing tolerance induction. Thus, normal cells of AKR.H-2^b, but not AKR.H-2^b:Fv-1^b, mice as young as three weeks displayed target antigens for B6 antiviral CTL. Construction of various F₁ mice showed that the level of expression of virus-associated antigens was dependent on gene dosage effects by Fv-1 and the viral genes involved. The implication of these effects on the generation and specificity of antiviral CTL is discussed using (B6 X AKR.H-2^b)F₁ responders as a model. (CA-36860, ACS IM-256).

GENETIC VARIATION AMONG MOUSE STRAINS IN VIRAL INHIBITION OF PRODUCTION OF INTERLEUKIN (IL) ACTIVITY. Mark A. Wainberg and Soopayah Vydelingum. Lady Davis Institute, Jewish General Hospital, Montreal, Canada H3T 1E2.

Previous studies have shown that co-incubation of any of several different types of retroviruses with mouse spleen cells, in the presence of Concanavalin A, can lead to inhibition of the T cell mitogenic response that normally ensues. This effect is independent of infection and can be obtained with UV-inactivated as well as live virus particles. In an effort to understand the mechanistic basis for such unresponsiveness, we compared spleen cells from different mouse strains in terms of the ability of UV-treated Friend leukemia virus (virus:cell ratio of 10:1) to inhibit production of IL-1 and IL-2 activities in the presence of lectin. The results show that levels of IL-2 activity in culture supernatants were reduced by 60-90% in the case of cells derived from each of Balb/c, C3H and B10.A mice. In contrast, levels of IL-1 activity (as measured in a thymocyte assay) were reduced by 80% in the case of B10.A mice but only by 20-40% for each of C3H and Balb/c animals. When cultures of adherent cells (mostly macrophages) were studied for production of IL-1 activity, in the presence of virus, B10.A cells were inhibited by 90% while C3H and Balb/c cells were only inhibited by 30%. Experiments involving F1's, F2's, and appropriate backcrosses of B10.A and Balb/c mice indicated that at least two genetic loci were responsible for the observed differences in terms of viral inhibition of IL-1 production by adherent cells. The addition of purified IL-2 to cultures of virus co-incubated spleen cells restored Con A-induced mitogenesis to near-control levels in each case tested, without significantly affecting levels of IL-1 activity. The addition of exogenous IL-1, in contrast, successfully restored both mitogenic potential as well as IL-2 levels. These data show that retroviral inhibition of T-lymphocyte mitogenesis apparently occurs as a consequence of interference with the production of IL-1 and IL-2. However, T cell sub-populations in the respective cultures remain responsive to both IL-1 and IL-2, even in the presence of viruses and despite the production of limited quantities of IL-1 and IL-2 activities.

LOW SUSCEPTIBILITY TO RETOVIRUS-INDUCED LYMPHOMAS OF SPONTANEOUSLY HYPERTENSIVE RATS WITH THYMIC DYSFUNCTION. Noritoshi Takeichi and Hiroshi Kobayashi, Cancer Institute, Hokkaido University School of Medicine, Sapporo 060, Japan.

We compared the incidence of lymphomas induced by Gross leukemia virus (GLV) between spontaneously hypertensive rats (SHR) with a congenital thymic dysfunction and normal Wistar (W) rats, the original strain of SHR. This SHR strain which has been established as an animal model for essential hypertension in humans possessed a decreased absolute number of T cells and revealed a selective depression T cell functions associated with an early appearance of natural thymocytotoxic autoantibody and a deficiency of thymic humoral factors. In particular, the numbers of rosette-forming thymocytes were markedly suppressed early in life.

When SHR were injected neonatally with GLV, only 3 out of 20 rats (15%) died with thymic lymphomas about 100 days after the virus infection and the remaining 17 rats survive more than 6 months without any clinical symptoms. In contrast, 27 out of 28 W rats (96%) developed lymphomas of mostly thymic origin about 90 days after the virus infection. The 3 lymphomas derived from the SHR bore only a Thyl.1 antigen, whereas most of the lymphomas derived from W rats carried not only a Thyl.1 antigen but also a guinea pig red blood cell rosette receptor and T antigens (W3/13 and W3/25). Grafts of 1-week-old male W thymus into the neonatal female SHR promoted a differentiation of thymocytes, restored T cell functions and significantly increased the incidence of the lymphomas which were positive for a rosette receptor and T antigens. Sex chromosomal analysis indicated that all these lymphomas tested were of host origin. Grafts of 1-week-old SHR thymus, however, failed to promote a differentiation of thymocytes and to increase the incidence of the lymphomas.

These results suggest that the low incidence of GLV-induced lymphomas in SHR may correlate closely with the absence or decreased numbers of the rosette-forming thymocytes which are presumably the target cells for GLV.

HLA ANTIGENS-LINKED GENETIC CONTROL IN SUSCEPTIBILITY AND RESISTANCE TO INFECTION. Gilles Lamoureux,* Pierre Duquette,** and Louise Labrie.* *Institut Armand-Frappier, Laval, Quebec H7V 1B7 and **MS Clinic, Notre-Dame Hospital, Montreal, Quebec, Canada.

Patients with multiple sclerosis (MS) from the two Montreal MS clinics, were divided into two groups: one group of 61 patients (MS type I) who had no clinical history of susceptibility to recurrent respiratory tract infections and a second group of 58 patients (MS type II) who had persistent susceptibility to such infections since childhood. All patients were typed for the HLA tissue antigens. The HLA antigen frequencies of the total MS patient population, and of MS type I and MS type II patients were compared to those of a normal control population and each other. The HLA-DR2 and B7 antigen frequencies were significantly increased compared to the normal controls for all MS patients. MS type I patients had an increased frequency for HLA-Bw42 and DRw8 antigens; the frequency of HLA-A29 was lower than in the controls and MS type II patients. MS type II patients had a significantly increased frequency for DR3 and some HLA-DR3-associated phenotypes (A1 + DR3; B8 + DR3; A1 + B8 + DR3) as compared to controls and MS type I patients. These results are consistent with the existence of genes linked to the HLA antigens, such as immune response genes, which control the resistance or susceptibility of the patients to infection, and suggest that these HLA antigens could be associated with a difference in the evolution of MS, as observed in the MS type I and II patients (J. Neurol. 230:81-90, 1983)

HYBRID SUSCEPTIBILITY TO MPC-11: POSSIBLE ROLE OF G_{IX} . Mary Clare Walker*, Mark A. Marsilli**, and Julia M. Phillips-Quagliata** *Institut Armand-Frappier, Laval, Quebec H7V 1B7 and **New York University Medical Center, New York, NY 10016.

The BALB/c plasmacytoma MPC-11 expresses the Murine Leukemia virus gp70 determinant G_{IX} , which is also a thymocyte differentiation antigen in some mouse strains. We already know that BALB/c mice and F_1 hybrids between BALB/c and its congenic resistant partners, all G_{IX}^- , are fully susceptible to MPC-11. All other hybrids susceptible to MPC-11, those between BALB/c and A, DBA/2, and SJL, are however G_{IX}^+ . Of resistant hybrids with C57BL/10, C57BL/6 (B6), C57L, DBA/1 and AKR, only the AKR x BALB/c F_1 is G_{IX}^+ . This suggested that G_{IX} might contribute to susceptibility, an idea which appeared to be confirmed by our finding that B6. G_{IX}^+ and 129 (G_{IX}^+) hybrids were significantly more susceptible to MPC-11 than their B6(G_{IX}^-) and 129. G_{IX}^- congenic partner hybrids. Backcross studies indicated that A mice lack any genes for resistance, B6 have 2 genes for resistance, and B6. G_{IX}^+ mice have only one gene, implying that one of the B6 genes was lost in deriving the B6. G_{IX}^+ strain, conceivably because it is linked to Gv-1 or Gv-2, the genes controlling G_{IX} expression. The possibility that G_{IX} is tolerated by G_{IX}^+ hybrids but is a relevant antigen for resistance in G_{IX}^- hybrids seems ruled out by our finding that the cytotoxic T lymphocyte (CTL)-mediated lysis of MPC-11 targets is not blocked by G_{IX}^+ thymocytes of appropriate H-2 type. In vivo susceptible hybrids such as (BALB/c x A.BY) F_1 s, although G_{IX}^+ , generate an in vitro anti-MPC-11 CTL response and splenocytes of H-2 matched G_{IX}^+ and $-$ strains which show normal anti-YAC-1 Natural Killer (NK) activity have very low NK activity against MPC-11 targets. Supported by ACS grant IM-213C and in part by IAF Research Funds.

HOST RESISTANCE DIRECTED SELECTIVELY AGAINST H-2
LOSS LYMPHOMA VARIANTS - ANALYSIS OF THE
MECHANISM AND IMPLICATIONS FOR THE INTERPRETATION
OF "HYBRID RESISTANCE" AND RELATED PHENOMENA.

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Three independent variants with a profound reduction of cell surface H-2 have been selected from the C57BL/6 mouse derived RBL-5 and EL-4 T-lymphomas. After subcutaneous inoculation of low cell doses in syngeneic mice, the H-2 negative variants failed to grow out whereas the wild type control lines showed progressive growth. No difference in growth rate or cloning efficiency was detectable in tissue culture. The outgrowth difference remained after the H-2 low variant and the control line had been injected subcutaneously in the opposite flanks of the same mouse whether normal or athymic nude mice were used. When mice were pretreated with anti-asialo GM1 antiserum both the control line and the H-2 negative variant showed progressive growth in vivo. Experiments comparing the distribution and survival of isotope prelabeled variant and wild type cells indicated that a rapid elimination of the former took place within 24 hours after i.v. injection. These differences in tumor elimination was not seen in mice treated with anti-asialo GM1 antiserum

It is concluded that the reduced tumorigenicity of sublines with impaired H-2 expression is largely, if not exclusively due to rapid elimination by NK cells. One possible explanation is that MHC encoded gene products are directly involved in a regulatory signal in the NK cell system. According to this interpretation, immunological selectivity in the NK cell system would be achieved by the failure to recognize self MHC, irrespective of the presence of foreign antigens, i.e. by detection of no self rather than non self. This may also explain previous observations on H-2 linked hybrid resistance against lymphoid grafts and changes in H-2 phenotypes associated with tumor progression.

REDUCTION IN HYBRID RESISTANCE TO PARENTAL BONE MARROW BY GRAFT VS. HOST INDUCED IMMUNODEFICIENCY. Frances T. Hakim and Gene M. Shearer, National Cancer Institute, Bethesda, MD 20205

Lethally irradiated F₁ mice that are heterozygous at H-2D reject bone marrow grafts from H-2^b parents, a phenomenon termed hybrid resistance (HR) (Cudkowitz G. and Nakamura S., Transplantation Proceedings, 15:2058, 1983). Multiple injections of H-2^b parental spleen cells into F₁, prior to marrow grafting, results in abrogation of HR ("tolerance" -- Cudkowitz G. and Bennett M., J. Exp. Med. 134:1513, 1971). We have investigated whether this phenomenon of parental-induced abrogation of HR is due to graft-vs-host (GVH) induced immunodeficiency. We have observed that injection of H-2^b parental spleen cells (C57Bl/10 or C57Bl/6) results in the inhibition of hybrid resistance in F₁ mice (B10xB10.BR)F₁, B₆D₂F₁ and B₆C₃F₁, as determined by the ¹²⁵I-IUDR spleen incorporation assay. This abrogation of HR has been observed in mice irradiated and injected with H-2^b parental bone marrow from 2 to 12 weeks after a single intravenous injection of parental spleen cells. The inhibition is cell dose dependent, with greatest effect observed at inocula of parental cells that produce GVH associated immunodeficiency, as determined by decreased capacity to generate cytotoxic T lymphocytes to allogeneic and hapten modified syngeneic targets. In view of recent reports that complete depletion of T cells can result in increased frequency of failure of human bone marrow engraftment (Martin M. et al., 10th Int'l Cong. Transplantation Society, 249, 1984), it is possible that GVH induced immunodeficiency can modulate hemopoietic graft rejection and that parental-induced "tolerance" to HR is the result of GVH.

TOWARDS A MECHANISM FOR HYBRID RESISTANCE TO THE BALB/c PLASMACYTOMA, MPC-11. J.M. Phillips-Quagliata, M.C. Walker and M.A. Marsili. New York University Medical Center, New York, N.Y. 10016.

(BALB/c X C57BL/10)F₁ (B10 F₁) hybrid mice resist doses of viable MPC-11 cells to which H-2 matched (BALB/c X BALB.B)F₁ (BALB.B F₁) hybrid mice are as susceptible as BALB/c mice themselves. We have previously shown resistance to be radiation-sensitive, intravenous silica-resistant and under the control of a single, dominant, autosomal gene that is not linked to the H-2 complex of B10 mice. We now show that resistance is not due to elevated NK cell activity, to antibody-dependant cell-mediated cytotoxicity or to increased F₁ anti-parental cytotoxicity on the part of B10 F₁ hybrids. Rather, it appears to be mediated by MPC-11-immune T cells, most likely cytotoxic T lymphocytes (CTL). Paradoxically, however, both spleen and lymph node cells from susceptible BALB.B F₁ hybrid mice make anti-MPC-11 CTL responses in vitro that are just as high as those made by lymphoid cells from resistant B10 F₁ hybrid mice, whether they are unprimed or taken early (up to 2 weeks for spleen cells or 1 week for lymph node cells) after tumor challenge. Suppression of the ability to generate a CTL response appears in the spleens of BALB.B F₁ hybrids later after tumor challenge, by which time large subcutaneous tumors are palpable. The suppression is mainly due to adherent cells although a Thy 1.2+ suppressor cell can also be detected. Suppression can be abrogated by pretreatment of the mice before tumor inoculation with Cyclophosphamide but this pretreatment does not protect the mice. This observation plus the fact that suppression is manifested too late after tumor implantation to account for the differences in tumor growth in susceptible versus resistant hybrids suggests this form of suppression to be a concomitant of tumor growth rather than its cause. We believe that the B10 gene for resistance facilitates either the delivery of effector cells to the site of tumor implantation or the maintenance of effector cell function in vivo. Supported by ACS grant No IM 213.

GENETIC CONTROL OF RESISTANCE TO LEUKEMIA GROWTH IN BNML-THE BEST RODENT MODEL FOR ACUTE (PRO-)MYELOCYTIC LEUKEMIA IN MAN. R. Michael Williams, Northwestern University Medical School, Chicago, IL 60611 and Boston University Medical School, Boston, MA 02118.

I have been enamoured with the Brown Norway Myelocytic Leukemia (BNML) model in rats because it so closely resembles clinical acute leukemia of man. Induced by 9,10-dimethyl 1,2-benzanthracene in a female BN, this tumor has cytology and cytochemistry equivalent to AProML. There is a slow growth rate due to a low growth fraction (40%) and high cell loss rate (up to 90%). Normal hemopoiesis is suppressed, disseminated intravascular coagulation (DIC) occurs and leukemic clonogenic cells can be detected in culture. Continuous cell lines have been derived. We first observed a genetic hybrid effect for natural killer cell activity against DNA virus induced BN fibrosarcoma PyB4 (Transplantation 23:283, 1977) and now have extended these studies to BNML. Bone marrow transplantation (BMT) studies showed that Lewis>LBNF1 rat radiation chimeras showed marked resistance to BNML compared to BN>F1 or F1>F1 controls. All animals were free of acute GVHD. Irradiated WFBNF1, LBNF1, and Lewis, but NOT BN or BNDAF1 rats resist transplantation of BN bone marrow as measured by ^{125}I UdR uptake. The genetics of median survival time (MST) after injection of BNML paralleled that of bone marrow transplantation. RT1(MHC) homozygosity was required for optimal immunogenicity of marrow--a direct analogy to Hh loci in mice. LBNF1 rats had MST of 50 days compared to 30 days in BNDAF1 and BN animals. This difference in MST corresponds to approximately 4 logs of leukemia cell reduction. LBNF1 rats injected with varying doses of BNML or PyB4 s.c. were not protected against 10^5 BNML given one year later. However, animals initially given 10^3 , 10^4 or 10^6 , but NOT 10^5 BNML died of leukemia before challenge at one year. We suspect that BNML can "immunize" against subsequent leukemia even though others have concluded that it lacks antigenicity. We propose that there are genetic determinants of immunogenicity and responsiveness to leukemia. Now we have generated several Lewis x BN recombinant inbred lines to help map such genes.

YAC-1 MHC CLASS I VARIANTS REVEAL AN ASSOCIATION BETWEEN DECREASED NK-SENSITIVITY AND INCREASED H-2 EXPRESSION FOLLOWING INTERFERON TREATMENT OR IN VIVO PASSAGE.

Gerald E. Piontek, Kazuto Taniguchi, Hans-Gustaf Ljunggren, Alvar Grönberg, Rolf Kiessling, George Klein and Klas Kärre, Depts. of Tumor biology and Immunology, Karolinska Institute, Stockholm, Sweden.

Two H-2 negative variants of the YAC-1 lymphoma were selected by mutagenization and sequential in vitro selections and compared to the wild type cells for changes in NK-sensitivity and H-2 expression following interferon treatment or in vivo passage. The H-2 negative variants and the wild type YAC-1 (H-2 positive, but low cell surface density of the antigen) had similar NK-sensitivity. However, beta- or gamma-interferon pretreatments increased the H-2 expression of YAC-1 control cells and protected them from NK-lysis, whereas the variants remained H-2 negative and NK-sensitive. The H-2 variants were similarly susceptible as control cells to three other cellular effects of interferon: protection from lytic VS-virus infection, modulation of Con A capping, and inhibition of cell proliferation. The wild type YAC-1 line also showed an increase in H-2 expression and a decrease in NK-sensitivity after in vivo passages (ascites) in irradiated mice. In contrast, in vivo passaged variant cells showed no reexpression of H-2 and remained NK-sensitive. The cell dose required to obtain organ colonization and malignant growth after intravenous injection was at least 1000 fold higher for the H-2 negative variants.

These results suggest that MHC Class I antigens may be required for interferon dependent modulation of the NK-sensitivity phenotype, as well as for expression of the malignant phenotype in the autologous host.

NATURAL RESISTANCE TO MOLONEY LYMPHOMA (YAC) ISOGRAFTS.
SELECTIVE INTRODUCTION OF RESISTANCE GENES DERIVED FROM
CBA, C₅₇L or C₅₇Bl/6 ON STRAIN A/Sn BACKGROUND.

Lars Åhrlund-Richter, Christer Nordstedt, Eva Klein
and George Klein. Department of Tumor Biology, Karolinska
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The murine lymphoma YAC, induced by Moloney virus in strain A/Sn, is highly sensitive to "hybrid resistance" in F₁ crosses between A/Sn and CBA, C₅₇L or C₅₇Bl/6. By using graded cell numbers for grafting, a critical cell dose can be found that grow in A/Sn mice but is rejected in the majority of the F₁ hybrid mice.

For the analysis of the genetics and the immunological mechanisms of this resistance we are developing a series of congenic resistant strains on A/Sn background.

F₁ hybrids between A/Sn and CBA, C₅₇L or C₅₇Bl/6 were back-crossed to A/Sn and the offspring challenged with a small inocula of YAC cells. Resistant mice were further back-crossed to A/Sn, followed by repeated YAC challenge and back-crossing.

The results with the back-cross populations showed that both H-2-linked and non-H-2-linked genes were able to determine resistance.

However, in the majority of the selections (12/16) non-H-2-linked resistance genes were selectively fixed. The presence of at least two independently segregating non-H-2-linked resistance genes was indicated.

Some of the selection lines have maintained a high NK activity, whereas others have lost it, in spite of succesful selection for in vivo resistance. Thus, at least two different resistance mechanisms may have been fixed in the existing lines. Further detailed effector analysis is in progress.

LUNG COLONIZATION AND METASTASIS BY DISSEMINATED B16 MELANOMA CELLS: H-2 ASSOCIATED CONTROL AT THE LEVEL OF THE HOST AND THE TUMOR CELL. Kazuo Iannuzzi, George Klein and Klas Kärre, Dept. of Tumor Biology, Karolinska Institute, Stockholm, Sweden.

Experimental metastasis of H-2⁺ and H-2⁻ B16 melanoma sublines was studied in H-2^{b/b} and H-2^{d/b} hosts by enumerating pulmonary colonies 20-40 days after i.v. inoculation of tumor cells. In H-2^{b/b} hosts, the H-2⁺ "B16-S" cells gave rise to a moderate number of metastatic colonies (6.3[±]6). The "B16-L" sublines that had lost the expression of MHC class I antigens according to RCG analysis and quantitative absorption tests, gave no metastases under the same conditions. Pretreatment of the H-2⁺ B16-S with interferons (beta or alpha + beta) increased their H-2 expression and the number of metastatic colonies (25[±]16). Interferon pretreatment of B16-L cells partially restored their H-2 expression and induced them to form a small number of metastatic colonies (1-4) in the majority of mice. The reduced pulmonary colonization by the H-2 negative B16-L cells could be attributed to their rapid elimination by natural killer cells, observed within 24 h after inoculation of radiolabelled cells. H-2⁻ B16 cells were more susceptible than H-2⁺ B16-S cells to in vitro lysis by poly I:C treated splenocytes and they were fully metastatic in hosts treated with anti-asialo GM-1 serum. In H-2^{d/b} heterozygous hosts, neither H-2⁺ nor H-2⁻ B16 cells were able to metastasize. Reduced pulmonary colonization by H-2⁺ B16-S cells was evident by 24 h after injection in comparison with H-2^{b/b} hosts, and could be reversed by anti-asialo-GM-1 treatment of the hosts. In vitro, H-2^{d/b} splenocytes were more cytotoxic to the B16-S cell than the syngeneic H-2^{b/b} effectors.

The results indicate that B16 H-2^{b/b} cells failed to metastasize whenever they had a quantitatively reduced or incomplete expression of the H-2 antigens in the host environment. This may be explained by a host surveillance mechanism directed specifically against cells which fail to express autologous "H" antigens adequately.

REGULATION OF EXPRESSION OF A CROSS-REACTIVE IDIOTYPE ON NORMAL AND MALIGNANT B CELLS: GENETIC CONTROL BY THE H-2 COMPLEX. Gail A. Bishop and Geoffrey Haughton, Department of Microbiology and Immunology, The University of North Carolina, Chapel Hill, N.C. 27514.

The double congenic mouse strain B10.H-2^aH-4^bp/Wts (2^a4^b) is highly susceptible to lymphomagenesis following adoptive hyperimmunization with sheep erythrocytes (SRBC). Of the 27 transplantable B cell lymphomas (CH lymphomas) derived from this strain, 22 bear surface immunoglobulins (sIg) which are idiotypically cross-reactive (CHIdX). The present study was designed to determine if CHIdX is present on normal splenic B cells of 2^a4^b mice, and to examine the genetic control of this restricted subset of B cells. We found that the spleens of normal 2^a4^b mice contain mitogen-responsive, Ly-1 positive cells which secrete hemolytic antibody specific for an antigen present on both SRBC and bromelain-treated mouse erythrocytes, a specificity shared by the sIg of six CH lymphomas. Approximately 50% of these cells bear sIg of the same idio- type as one of these six lymphomas, CH12. Expression of this idio- type did not correlate with Igh-1 allotype, and backcross analysis demonstrated H-2 regulation of the frequency of the idio- type-positive B cell. Analysis of 22 inbred mouse strains, including several congenic pairs, mapped the influential gene to the I-E subregion. Only mouse strains homozygous for E_a^K showed idio- type expression, which was a recessive trait. It is hypo- thesized that defective control of proliferation of CHIdX-bearing B cells in 2^a4^b mice may influence their susceptibility to lymphomagenesis.

METHODOLOGY FOR TESTING THE HYPOTHESIS OF SINGLE LOCUS CONTROL OF HOST RESISTANCE. Jill Curtis, C.F. Curtis and M.H. Barton, University of London, London, U.K.

Resistance of mice to various pathogens has recently been attributed to alleles at single loci on the basis of crosses and backcrosses between inbred strains. Resistance and susceptibility are generally not absolute but are measured on some quantitative scale such as time to death or pathogen density. Where the distributions of the parental strains and F1 hybrids do not overlap, single locus control of resistance leads to bimodal distributions in the backcross progenies, whereas multigenic control leads to unimodal backcross progenies. Where the parents and F1s are less distinct, unimodality may be the expectation with either form of genetic control. In any case, one expects a 1:1 ratio of backcross individuals on either side of the mid-point between the means of the F1 and parental strain and it is a mistake to conclude from finding such a 1:1 ratio that single locus control is necessarily operating. On the single locus hypothesis, one can make a detailed prediction of the distribution of the backcross progeny from the superimposition of the observed distributions of the F1 and parental strain. If the observed data deviate significantly in the direction of a greater concentration in the middle range, one can conclude that more than one locus is having an effect on resistance. A maximum likelihood method for testing the goodness of fit to the single locus hypothesis or various multilocus hypotheses is demonstrated using examples from the literature.

THE Ity/Lsh/Bcg GENE SIGNIFICANTLY AFFECTS MOUSE RESISTANCE TO MYCOBACTERIUM LEPRÆMURIUM. I.N.Brown and A.A.Glynn, St Mary's Hospital Medical School and Central Public Health Laboratory London.

We have shown previously (Brown, Glynn and Plant 1982) that resistance of inbred mice strains given Mycobacterium lepraemurium intravenously broadly follows the Ity/Lsh/Bcg pattern. However within the resistant group the strains ranked in a different order to that shown with Salmonella typhimurium showing the influence of other genes. Further experiments confirm that Ity has a role in resistance to M. lepraemurium. Because of the long survival times (over 200 days in some strains) resistance was measured by counting the numbers of intact acid fast bacilli in the spleens of mice 8 weeks after intravenous injection of a standard inoculum as described by Brown & Krenzien (1976). The method showed a clear difference in resistance to M. lepraemurium between Ity^r & Ity^s strains. Two Ity^r strains not tested previously, A and C57L were resistant to M. lepraemurium. In the previous paper only female mice were used. It now became clear that male mice were usually less resistant than their female genetic counterparts. Resistance was dominant in the F1 generations of BALB/c x CBA, CBA x BALB/c and BALB/c x C57L crosses. In the F2 generation of the BALB/c x C57L cross, resistance segregated with the leaden gene. Dr J. Blackwell kindly allowed us to test some of her congenic strain B.10.Lsh^r which contains the Lsh/Ity gene on a B10. background and has been shown to be resistant to Leishmania donovani and S. typhimurium. Both the homozygous and heterozygous (B10 x B10.Lsh^r) strains were resistant to M. lepraemurium. The Ity/Lsh/Bcg gene, which is on chromosome 1, therefore plays a part in resistance to M. lepraemurium.

THE EFFECT OF THE Bcg GENE ON THE EARLY HOST RESPONSE TO INFECTIONS WITH BCG SUBSTRAINS AND ATYPICAL MYCOBACTERIA. Michel Denis¹, Adrien Forget¹, Micheline Pelletier², Emil Skamene³ and Raymond Turcotte⁴. 1. Département de microbiologie et d'immunologie and 2. Département de Pathologie Faculté de Médecine, Université de Montréal, Québec, Canada; 3. Montreal General Hospital Research Institute, Montréal; 4. Bacteriology Research Center, Institut Armand Frappier, Québec, Canada.

The effect of Bcg gene on the early host response to intravenous infection to a variety of BCG substrains and some atypical mycobacteria was investigated. The infections were evaluated by the enumeration of CFU in the spleens and the splenomegaly response. Granulomatous hepatitis was also evaluated by enumerating liver granulomas. The number of BCG Pasteur and BCG Tice recovered from the spleens of Bcg^S (C57BL/6, B10.A and BALB/c) at 3 weeks following infection exceeded the original bacterial inoculums whereas the number of CFU recovered from the spleens of Bcg^r mice (A/J, DBA/2 et C3H/HeN) did not exceed the number of CFU injected, thus following the pattern observed in Bcg^S and Bcg^r mice infected with BCG Montreal. BCG Russia failed to multiply in both test groups, however the number of CFU recovered in Bcg^r mice was significantly lower than in Bcg^S mice. On the other hand, the number of CFU in the spleens of Bcg^r and Bcg^S mice injected with BCG Japan were undetectable in most cases. Involvement of Bcg gene in the early resistance to infection with BCG Pasteur and M. kansasii was shown by following the kinetics of infections in the C-D2 (BALB/c - Bcg^r) congenic line. However, in M. intracellulare and BCG Russia infections, the phenotypic expression of the Bcg gene was observed as a more rapid elimination of the bacteria in the spleens of C-D2 than in the susceptible BALB/c mice. On the other hand, following infections with BCG Pasteur and M. kansasii, granulomatous hepatitis appeared in relation not only with the bacterial load but also with the genetic background of the host. This last observation will be discussed.

ONLY TWO OUT OF FIFTEEN BCG STRAINS FOLLOW THE Bcg PATTERN.
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Saranac Lake, NY 12983

The growth of low dose intravenous inocula (10^4) of 15 type strains of M. bovis BCG and 2 strains of M. tuberculosis were followed in the spleens and lungs of 8 week old male C57BL/6 (Bcg^S) and DBA/2 (Bcg^r) inbred mice. Of the fifteen BCG strains tested only two (BCG Montreal and BCG Australian) grew in the spleens of Bcg^S and Bcg^r mice in a manner consistent with the Bcg gene effect. Of the other thirteen strains, ten grew well in the spleens of both the Bcg^r and Bcg^S mice, whilst another three (BCG Birkhaug, BCG Japan and BCG Glaxo) multiplied slowly in both groups of test animals. In contrast, only one strain of BCG tested (BCG Connaught) grew better in the lungs of Bcg^S mice than in the lungs of the Bcg^r animals. Both strains of M. tuberculosis (H37Rv, Erdman) grew equally well in the Bcg^S and Bcg^r strains of mice. The relevance of these observations to the theory of natural resistance to mycobacterial infections will be discussed in the context of recent findings in this laboratory in which the kinetics of emergence of acquired immunity in Bcg^r mouse strains to these infections has been determined.

GENETIC ANALYSIS OF SUSCEPTIBILITY AND RESISTANCE OF MICE TO TUBERCULOSIS INFECTION. Boris V. Nickonenko, Arcadyi M. Moroz, Alexander S. Apt and Mikhail M. Averbakh. Central Institute for Tuberculosis, Moscow, 107564, USSR.

The survival time of more than 20 mouse strains was examined after i.v. injection with M. tuberculosis virulent H37Rv strain (dose - 0.025 mg/mouse). Supersensitive I/St strain (median survival time, MST = 20.9 ± 1.5 d) and resistant A/Sn strain (MST = 56.5 ± 4.2 d) were revealed. The analysis of (A/Sn x I/St)F₁ hybrids and F₁ x I/St, F₁ x A/Sn backcross generations have shown by the segregation patterns that the supersensitivity of I/St is inherited as one Mendelian recessive autosomal trait, designated as Ts-1 and being not linked with H-2 (chr. 17) and s (piebald) gene (chr. 14). The relative resistance of A/Sn mice is determined by at least two genes, none of which is allelic to Ts-1. The phenotypic expression of these genes is repressed in Ts-1/Ts-1 homozygous mice, i.e. Ts-1 is epistatic trait. It's relation to Bcg gene in chr.1 yet remains unknown and is investigated now. The infection of (CBA x B6), (CBA x I), (B6 x BALB/c), (A x I), (B10.WB x I), (AKR x I) and (BRSUNT x I) F₁ mice shown that all these hybrids were much more resistant to tuberculosis if compared with their parents, with the exception of (BRSUNT x I)F₁ which had intermediate susceptibility. The MST of B6 and BALB/c strains is similar (27.2 ± 1.6 and 32.1 ± 1.4 d, respectively), while the hybrids B6F₁ are much more resistant (MST = 90.4 ± 4.4 d). This "hybrid effect" is under complicated genetic control because the infection of 7 RI CXB mouse strains revealed one resistant (CXBI, MST = 51.0 ± 2.1 d) and one susceptible (CXBD, MST = 25.0 ± 0.7 d) strain, other 5 being intermediate. The work was supported by WHO's INETUB programm.

CONTINUOUS EXPRESSION OF I-A BY MACROPHAGES CORRELATES WITH BCG RESISTANCE. Bruce S. Zwillig, Sarah Johnson, Linda Vespa and Mike Kwasniewski. The Ohio State University, Columbus, OH 43210.

The expression of I-A by macrophages is important for the induction of an immune response. We induced the expression of I-A by peritoneal injection of Mycobacterium bovis (strain BCG) or Listeria monocytogenes. When peritoneal macrophages from C3H/HeN mice were obtained 7 days after the injection of 10^4 microorganisms, I-A was transiently expressed as determined by indirect immunofluorescence using an anti I-A^K monoclonal antibody. However, when macrophages were obtained from the peritoneal cavity 28 days after injection of the microorganisms, only the macrophages from the BCG injected mice continuously expressed I-A for up to 10 days of in vitro culture. The continuous expression was not due to the presence of antigen nor to contaminating lymphocytes. Continuous expression could be induced in vitro by exposure of resident macrophages to lymphokine. When we compared the kinetics of I-A expression on macrophages from different strains of mice, the continuous expression of I-A correlated with the genetic resistance of mice to BCG. Macrophages from mice that were resistant to BCG continuously expressed I-A while macrophages from BCG susceptible mice transiently expressed I-A. Injection of resistant mice with Salmonella typhimurium did not result in the induction of a population of macrophages that continuously expressed I-A suggesting that the Bcg gene may not be the same as that responsible for resistance to Salmonella (Ity). Supported by NCI grant CA31447.

GENETIC VARIATION IN PRODUCTION OF INTERFERON GAMMA IN BCG-SENSITIZED MICE CHALLENGED WITH PPD. Kris Huygen and Kamiel Palfliet, Instituut Pasteur van Brabant, 1040 Belgium

We have examined mouse strain variation in IFN- γ production of Bacillus Calmette-Guerin (BCG) sensitized mice, challenged with Purified Protein Derivative (PPD) of tuberculin. Heat inactivated or gamma irradiated BCG preparations were ineffective in inducing IFN- γ responses. Nude mice lacking functional T cells failed to produce IFN- γ and cyclophosphamide and especially 800 rad irradiation drastically reduced the IFN- γ levels obtained. C57Bl/6 mice were high producers for *in vivo* (serum) and *in vitro* (spleen cell culture) induced IFN, whereas BALB/c mice were found to be low producers under these two conditions. Studies on (BALB/c X C57Bl/6)F₁, F₂ and backcross generation mice, indicate that one partially dominant, autosomal locus is involved. Furthermore, females consistently produce more IFN than males, both in serum and in spleen cell cultures, but the X chromosome cannot be held responsible for this. (IFN levels in male animals from reciprocal F₁ crosses were not significantly different) Low IFN- γ levels in BALB/c mice seem not to be caused by classical suppressor T cells or macrophages, nor by inactivation of secreted IFN by inhibitory substances. Strain Distribution Pattern of CXB Recombinant Inbred strains was determined: D, H and J strains produce significantly lower IFN- γ levels than E, G, I and K strains, though low responder RI strains have always higher IFN titers than the parental BALB/c low producer. The SDP could be observed for both serum IFN levels as for spleen cell culture supernatant. C57Bl/6 mice congenic for the BALB/c H-36^c minor histocompatibility allele, had significantly lower levels of IFN than C57Bl/6 mice, especially at suboptimal doses of PPD. This indicates that a locus linked to H-36 or H-36 itself is involved in the regulation of BCG-PPD IFN- γ , but additional influences certainly exist. Examination of CB-20 mice, congenic for Igh^b allele on a BALB/c background, indicates that the immunoglobulin allotype also exerts a slight influence on the IFN level produced. The major histocompatibility complex H-2 seems not to be involved.

K. Huygen et al. Cell. Immunology, 85, 75-81, 1984.

GENETIC CONTROL OF TUBERCULIN DTH TIME COURSE IN MICE;
CORRELATION WITH NATURAL AND ACQUIRED RESISTANCE AGAINST
BCG. Bruno Hurltel, Maryse Hurltel*, and Philippe Lagrange,
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A significant PPD delayed-type hypersensitivity reaction (DTH) can be induced in mice after subcutaneous (SC) immunization with 4×10^6 Mycobacterium bovis strain BCG. Using this model and a strictly standardized procedure of elicitation and measurement of DTH, three investigations were successively undertaken : 1) PPD DTH time course was studied in inbred mice, F1 and F2 hybrids, in backcross mating mice and in outbred mice, 2) the DTH patterns characterized in groups of mice (strains, F1) or in individual mice (F2, backcross, outbred) were compared to the growth of BCG in draining lymph node (LN), 3) lastly these DTH patterns were compared to the acquired resistance by measuring in SC immunized mice the growth of BCG in spleen after IV injection of 10^4 , 10^5 or 10^6 BCG. Results shown that PPD DTH time courses were genetically controlled, each strain presenting a typical time pattern. These different patterns could be classified in three types : early, protracted and intermediary. The early type was dominant and appeared sooner after immunization. The protracted type was only found in susceptible strains as defined by Skamene and coll., but not in all susceptible strains, Balb/C giving an early type. No correlation was found between DTH type or DTH level and growth of BCG in footpad or LN after SC immunization with 4×10^6 BCG. However, when mice were SC inoculated with smaller doses of BCG, a lower multiplication rate occurred in draining LN in the resistant strains during the first days following challenge. On the other hand, some correlation can be shown between the protracted type and the DTH level measured 42 h after elicitation and the ability of SC immunized mice to inhibit in spleen growth of BCG IV injected.

Cellular Immune Response to Mycobacterium bovis (BCG) in genetically-susceptible and resistant congenic mouse strains. Diane Bourassa¹, Adrien Forget¹, Micheline Pelletier², Emil Skamene³ and Raymond Turcotte⁴;

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Congenic Bcg^r (C.D2), resistant and Bcg^s (BALB/c), susceptible mice were infected intravenously with Mycobacterium bovis (BCG, strain Montreal) in order to establish the relationship between different indicators of cellular mediated immune response and the bacterial load attained in the host. There was a correlation between the splenomegaly response, the granuloma formation in the liver, the cross-protection against an heterologous pathogen (Listeria monocytogenes) and the bacterial burden in Bcg^r and Bcg^s mice. No relationship was found between the bacterial load, the delayed footpad hypersensitivity and the development of specific acquired protection against an homologous organism (BCG or M. tuberculosis).

H-2-ENCODED CLASS II GENE PRODUCTS IN REGULATION OF IMMUNITY IN THE COURSE OF TUBERCULOSIS IN MICE. Alexander S. Apt, Arcadiy M. Moroz, Boris V. Nickonenko and Mikhail M. Averbakh, Central Institute for Tuberculosis, Moscow 107564, USSR.

The survival time of different mouse strains infected with M.tuberculosis H37Rv (0.025mg/an) and the proliferative responses in the presence of PPD and PHA of their lymph node cells in 48h cultures was studied. It was shown that the survival time (43.0 ± 2.4 d) and the level of specific proliferative response against PPD at the 10th day of infection ($20,348 \pm 943$ cpm) of 4R (K^kA^k) recombinant were significantly higher (31.7 ± 1.9 d and $14,314 \pm 1,218$ cpm, respectively) than these of B10 (K^bA^b) congenic mice. Treatment of cultures with anti-I-A^k monoclonal antibodies significantly diminished ($9,998 \pm 1,044$ cpm) the capacity of 4R cells to proliferate in the presence of PPD but neither decreased the level of their PHA-proliferation, nor affected PHA and PPD responses of B10 cells. This suggests that the specific immune response against PPD is under I-A genetic control and that I-A^k is "high-responder" while I-A^b - "low-responder" allele.

It was shown also that the development of the disease is accompanied with increasing suppression of specific (vs PPD) and nonspecific (vs PHA) proliferative responses in vitro in all mouse strains tested (A/Sn, I/St, B10, 4R, HTT, D2). The suppression is mediated, at least at some degree, by T cells as it was shown by adoptive transfer and anti-Thy-1.2 antiserum treatment. The specific alloantiserum (3R x DBA/2)F₁ vs 5R against the I-J^k-allele-product (I-J is the I-region-encoded universal marker of suppressor pathway of different immune responses with still illusive DNA material for it) was obtained, which, as it was shown by microcytotoxicity assay, reacts with I-J^k-positive but not with I-J^{b,d,s}-positive cells. The administration of

anti-I-J^k in infected recipients(two injections 15-17 mkl each at the days 0 and 1 of infection) decreased the level of both types of suppression as measured in vitro as well as the DTH reaction suppression against PPD in in vivo test and prolonged the survival time of I-J^A-positive but not I-J^k-negative mice. A reciprocal antibody, anti-I-J^b, obtained by immunization of (5R x DBA/2)F₁ recipients with 3R cells shows no cytotoxic activity with I-J^b targets and failed to decrease the level of suppression in B10 infected mice. Thus, the therapeutic activity of anti-I-J antisera correlates with their cytotoxic activity.

After vaccination with 1 mg of BCG mice of congenic B10, B10.A, B10.SJ, R107 and B10.M strains were infected with H37Rv virulent strain of M. tuberculosis within 6 wk interval. Vaccination significantly (P = 0.02) increased the survival time of all these mice, but B10.M. As the B10 mice are low-responders to PPD after primary infection and B10.M mice do not develop the protective immunity after BCG vaccination and both strains have the "silent allele" of I-E subregion of the H-2 complex, it could be assumed that I-E genes also play an important role in antituberculosis immunity.

Thus, we have obtained data which show that the H-2-encoded Class II antigenic structures determine at least some steps of protective and suppressive immune responses against M. tuberculosis. The work was supported by WHO's IMMTUB programm.

SINGLE LOCUS DIFFERENCE BETWEEN C57Bl/6 and C3H/He RESPONSIBLE FOR THE DEVELOPMENT OF ANAEMIA IN BCG INFECTED MICE.
Gilles Marchal and Geneviève Milon, Institut Pasteur, Paris.

Mice of different strains infected iv. with Bacille de Calmette et Guérin (BCG) exhibited two distinct patterns of response as determined by the decrease of packed cell volume found on day 14 after infection. The mouse strains were classed into mice which developed BCG-induced anaemia (C57Bl/6 type) and those without anaemia (C3H/He type).

It was previously shown that BCG-induced anaemia was secondary to a decrease in erythropoietic progenitor cells and was related to conditions which allowed the development of a protective immune response against BCG infection. The BCG-induced anaemia was found dependent upon the route, dose and viability of BCG injected but not upon the origin of BCG strain, Glaxo, Danish and French strains giving similar results. Numerations of BCG in C57Bl/6 and C3H/He mice eliminated a direct action of BCG growth in haemopoietic tissues.

A genetic analysis of the character, BCG-induced anaemia, was performed on F1, F2 and backcross derived from mating of C57Bl/6 and C3H/He. Anaemia was more important in female than in male mice showing a sex association without sex linkage (X linkage) as appreciated on F1 of the two mating combinations. The heterozygotes F1 were intermediate between the two homozygotes without dominance deviation. Environmental and genetic variances were approximately equivalent. According to variance analysis using three methods of calculation, the trait heritability was 0.55 and the number of loci 1 (0.87, 1.06, 1.15, 1.35, 1.42 and 1.84 being the calculated values).

BXH recombinant strains between C57Bl/6 and C3H/He were classed according to the percentage of packed cell volume decrease. Their distribution in either C57Bl/6 or C3H/He group supported also the preceding result that a single gene difference between the parental strains was associated with BCG-induced anaemia.

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1. CONTRATO DE ALUGUEL DE LOCAÇÃO DE IMÓVEL - 1996, 1997, 1998, 1999, 2000, 2001, 2002, 2003, 2004, 2005, 2006, 2007, 2008, 2009, 2010, 2011, 2012, 2013, 2014, 2015, 2016, 2017, 2018, 2019, 2020, 2021, 2022, 2023, 2024, 2025, 2026, 2027, 2028, 2029, 2030, 2031, 2032, 2033, 2034, 2035, 2036, 2037, 2038, 2039, 2040, 2041, 2042, 2043, 2044, 2045, 2046, 2047, 2048, 2049, 2050, 2051, 2052, 2053, 2054, 2055, 2056, 2057, 2058, 2059, 2060, 2061, 2062, 2063, 2064, 2065, 2066, 2067, 2068, 2069, 2070, 2071, 2072, 2073, 2074, 2075, 2076, 2077, 2078, 2079, 2080, 2081, 2082, 2083, 2084, 2085, 2086, 2087, 2088, 2089, 2090, 2091, 2092, 2093, 2094, 2095, 2096, 2097, 2098, 2099, 2100, 2101, 2102, 2103, 2104, 2105, 2106, 2107, 2108, 2109, 2110, 2111, 2112, 2113, 2114, 2115, 2116, 2117, 2118, 2119, 2120, 2121, 2122, 2123, 2124, 2125, 2126, 2127, 2128, 2129, 2130, 2131, 2132, 2133, 2134, 2135, 2136, 2137, 2138, 2139, 2140, 2141, 2142, 2143, 2144, 2145, 2146, 2147, 2148, 2149, 2150, 2151, 2152, 2153, 2154, 2155, 2156, 2157, 2158, 2159, 2160, 2161, 2162, 2163, 2164, 2165, 2166, 2167, 2168, 2169, 2170, 2171, 2172, 2173, 2174, 2175, 2176, 2177, 2178, 2179, 2180, 2181, 2182, 2183, 2184, 2185, 2186, 2187, 2188, 2189, 2190, 2191, 2192, 2193, 2194, 2195, 2196, 2197, 2198, 2199, 2200, 2201, 2202, 2203, 2204, 2205, 2206, 2207, 2208, 2209, 2210, 2211, 2212, 2213, 2214, 2215, 2216, 2217, 2218, 2219, 2220, 2221, 2222, 2223, 2224, 2225, 2226, 2227, 2228, 2229, 2230, 2231, 2232, 2233, 2234, 2235, 2236, 2237, 2238, 2239, 2240, 2241, 2242, 2243, 2244, 2245, 2246, 2247, 2248, 2249, 2250, 2251, 2252, 2253, 2254, 2255, 2256, 2257, 2258, 2259, 2260, 2261, 2262, 2263, 2264, 2265, 2266, 2267, 2268, 2269, 2270, 2271, 2272, 2273, 2274, 2275, 2276, 2277, 2278, 2279, 2280, 2281, 2282, 2283, 2284, 2285, 2286, 2287, 2288, 2289, 2290, 2291, 2292, 2293, 2294, 2295, 2296, 2297, 2298, 2299, 2300, 2301, 2302, 2303, 2304, 2305, 2306, 2307, 2308, 2309, 2310, 2311, 2312, 2313, 2314, 2315, 2316, 2317, 2318, 2319, 2320, 2321, 2322, 2323, 2324, 2325, 2326, 2327, 2328, 2329, 2330, 2331, 2332, 2333, 2334, 2335, 2336, 2337, 2338, 2339, 2340, 2341, 2342, 2343, 2344, 2345, 2346, 2347, 2348, 2349, 2350, 2351, 2352, 2353, 2354, 2355, 2356, 2357, 2358, 2359, 2360, 2361, 2362, 2363, 2364, 2365, 2366, 2367, 2368, 2369, 2370, 2371, 2372, 2373, 2374, 2375, 2376, 2377, 2378, 2379, 2380, 2381, 2382, 2383, 2384, 2385, 2386, 2387, 2388, 2389, 2390, 2391, 2392, 2393, 2394, 2395, 2396, 2397, 2398, 2399, 2400, 2401, 2402, 2403, 2404, 2405, 2406, 2407, 2408, 2409, 2410, 2411, 2412, 2413, 2414, 2415, 2416, 2417, 2418, 2419, 2420, 2421, 2422, 2423, 2424, 2425, 2426, 2427, 2428, 2429, 2430, 2431, 2432, 2433, 2434, 2435, 2436, 2437, 2438, 2439, 2440, 2441, 2442, 2443, 2444, 2445, 2446, 2447, 2448, 2449, 2450, 2451, 2452, 2453, 2454, 2455, 2456, 2457, 2458, 2459, 2460, 2461, 2462, 2463, 2464, 2465, 2466, 2467, 2468, 2469, 2470, 2471, 2472, 2473, 2474, 2475, 2476, 2477, 2478, 2479, 2480, 2481, 2482, 2483, 2484, 2485, 2486, 2487, 2488, 2489, 2490, 2491, 2492, 2493, 2494, 2495, 2496, 2497, 2498, 2499, 2500, 2501, 2502, 2503, 2504, 2505, 2506, 2507, 2508, 2509, 2510, 2511, 2512, 2513, 2514, 2515, 2516, 2517, 2518, 2519, 2520, 2521, 2522, 2523, 2524, 2525, 2526, 2527, 2528, 2529, 2530, 2531, 2532, 2533, 2534, 2535, 2536, 2537, 2538, 2539, 2540, 2541, 2542, 2543, 2544, 2545, 2546, 2547, 2548, 2549, 2550, 2551, 2552, 2553, 2554, 2555, 2556, 2557, 2558, 2559, 2560, 2561, 2562, 2563, 2564, 2565, 2566, 2567, 2568, 2569, 2570, 2571, 2572, 2573, 2574, 2575, 2576, 2577, 2578, 2579, 2580, 2581, 2582, 2583, 2584, 2585, 2586, 2587, 2588, 2589, 2590, 2591, 2592, 2593, 2594, 2595, 2596, 2597, 2598, 2599, 2600, 2601, 2602, 2603, 2604, 2605, 2606, 2607, 2608, 2609, 2610, 2611, 2612, 2613, 2614, 2615, 2616, 2617, 2618, 2619, 2620, 2621, 2622, 2623, 2624, 2625, 2626, 2627, 2628, 2629, 2630, 2631, 2632, 2633, 2634, 2635, 2636, 2637, 2638, 2639, 2640, 2641, 2642, 2643, 2644, 2645, 2646, 2647, 2648, 2649, 2650, 2651, 2652, 2653, 2654, 2655, 2656, 2657, 2658, 2659, 2660, 2661, 2662, 2663, 2664, 2665, 2666, 2667, 2668, 2669, 2670, 2671, 2672, 2673, 2

To search for a genetic component of susceptibility to leprosy, family and marker studies were undertaken in a small caribbean island (Mésirade) where leprosy is highly prevalent (2.5%). Pedigree data, ascertained through all leprosy patients living in the island in 1987, were established and checked for correct parentage. Genetic analysis was performed on 16 large pedigrees comprising a total of 62 leprosy patients classified as lepromatous (26) and non-lepromatous (42), to simplify the analysis. The possible segregation of two alleles at an autosomal susceptibility locus was investigated using the transmission probability model taking into account a variable age of onset of the disease (computer program GENPED). The small size of the island and the living conditions allowed us to assume a uniform contact with *M. leprae* for all individuals. The lepromatous and non-lepromatous forms were analyzed separately and together. When the non-lepromatous form is considered separately, the hypothesis of a recessive susceptibility gene segregating is compatible with the data. However, in our all other analyses, there is evidence for some kind of genetic transmission of the host response to infection which can not be accounted for by a simple Mendelian inheritance.

Gm and Km immunoglobulin allotypes were determined for the entire population (about 1,000 persons over 5 years of age) as part of an extensive genetic population survey. HLA typing was performed in 139 persons, specially leprosy patients and those sharing their household. The comparison of the distribution of these marker phenotypes between unrelated leprosy patients (18 for HLA, 26 for Gm and Km) and controls (27 unrelated individuals for HLA, the whole population for Gm) did not show any significant difference, except a slight increase of HLA-A2 antigen in leprosy patients. It was not possible to analyze the segregation of parental HLA or Gm haplotypes among affected sib pairs since there were few pairs with both members still living at the time of the study.

By using a number of different inbred mouse strains with their relative ability to recruit inflammatory neutrophils and macrophages to the peritoneal cavity in response to an i.p. injection of various sterile irritants, there is very little available information, however, on the comparative ability of listeria-resistant and susceptible strains of mice to develop T cell-mediated enhanced resistance to listeriosis after being immunized by a sublethal listeria infection. In this study, we report that listeria-resistant C57BL/6 and listeria-susceptible A/J mice both demonstrate enhanced clearance of a secondary listeria challenge from the spleen, but that complete elimination of viable listeria occurs more rapidly in C57BL/6 than in A/J mice. Immunized C57BL/6 mice more rapidly accumulate inflammatory peritoneal neutrophils in response to the i.p. injection of dead listeria than do A/J mice; however, similar numbers of inflammatory peritoneal macrophages accumulate in the two mouse strains. Both C57BL/6 and A/J mice were able to generate spleen T cells capable of transferring to syngeneic recipients both resistance to listerial infection and enhanced accumulation of inflammatory peritoneal phagocytes in response to i.p. injection of dead listeria. These results suggest that a primary sublethal listeria infection in susceptible A/J mice establishes a state of enhanced immunoresponsiveness that is able to compensate at least in part for the deficient innate resistance of these mice.

RESISTANCE TO LISTERIOSIS IN TWO LINES OF MICE
GENETICALLY SELECTED FOR HIGH AND LOW ANTIBODY PRODUCTION.
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Infection by the intracellular parasite Listeria monocytogenes was studied in two inbred lines of mice genetically selected by G. Biozzi and coworkers for high and low antibody production against xenogeneic red blood cells. It was found that the innate resistance to listeriosis was similar in low responder (LR) and high responder (HR) mice, as shown by the LD50 values respectively estimated as 2.2×10^5 and 3.8×10^5 bacteria per mouse. This natural resistance was expressed at the same level as that of C57BL/6 mice, suggesting that both HR and LR mice might harbor the genes "Lr" of resistance to L. monocytogenes. After sublethal systemic infection, the kinetics of bacterial growth in the spleen and the liver was almost identical in the two lines after day 2 of infection, indicating that mice from both lines generated efficient anti-Listeria immunity. However, it was revealed that during the early non specific phase of infection, bacterial growth in tissues was significantly enhanced in HR mice. This is interpreted as the in vivo expression of a genetic impairment of the bactericidal activity of resident macrophages in this line of mice. This genetic failure in macrophage activity resulted in a significant increase of anti-Listeria antibody production in HR mice, and did not prevent T-dependent activation of effector macrophages mobilized in infectious sites. No interline difference was observed in the expression of T cell-mediated immunity, as estimated by the production of protective T cells and delayed sensitivity T cells, and by the level of immunological memory. The meaning of these results will be discussed.

SERUM AMYLOID P-COMPONENT (SAP) RESPONSE OF IMMUNE MOUSE STRAINS DURING LISTERIA MONOCYTOGENES INFECTION. Prati P. Singh and Richard F. Mortensen, Dept. of Microbiology, Ohio State Univ., Columbus, Ohio 43210.

The acute phase of the systemic inflammatory response to infection in mice is marked by an increase in the levels of serum amyloid P-component (SAP), the major acute phase reactant of mice. The SAP levels of infected mouse strains were measured 48 hrs after infection with L. monocytogenes. Sensitive strains (Ls) had up to a 32-fold increase in their SAP levels, while resistant strains (Lr) showed only a 6-fold increase. A mouse strain with intermediate susceptibility (CE6F1) had a 25-fold increase in SAP. Immune C3H/HeJ (Ls) mice with only 1% of the bacterial burden of nonimmune mice displayed a 16-fold increase in SAP. The SAP response was proportional to the organ burden of *Listeria* in all strains. Purified mouse SAP and its human analogue, C-reactive protein (CRP), slightly enhanced the in vitro listericidal activity of macrophages from Lr and Ls strains. Exogenously added SAP and CRP could bind to 45% of elicited macrophages. SAP did not alter the in vitro listericidal activity of immune macrophages. SAP also did not alter the listericidal activity of macrophages from unimmunized Lr mice that were elicited with heat killed L. monocytogenes. Similarly elicited macrophages from immune Ls mice displayed high listericidal activity (60-90%) that was not altered by added SAP. The results are consistent with SAP serving as a sensitive marker and gauge of acute bacterial infection; however, SAP appears to have very limited activity as an effector or regulatory protein in the macrophage-mediated nonspecific antibacterial response. (Supported by USPHS grant CA-30015).

VARIATION IN BACTERICIDAL ACTIVITY OF MACROPHAGES FROM LISTERIA-RESISTANT AND -SUSCEPTIBLE MOUSE STRAINS. Francine Gervais and Emil Skamene, Montreal General Hospital Research Institute, Montreal, Quebec H3G 1A4.

Innate resistance to Listeria monocytogenes (Lm) infection is genetically controlled and involves an augmented inflammatory response. In vivo macrophage-mediated listericidal activity is difficult to interpret because of heterogeneity of the peritoneal exudate. Macrophage-mediated listericidal activity of resistant C57BL6/J (B) and susceptible A/J (A) mouse strains was determined in vitro using a temperature-sensitive mutant. When peritoneal resident macrophages from resistant B and susceptible A mice were tested, both strains had similar in vitro listericidal activity. Peritoneal inflammatory macrophages from B mice showed a 3 fold greater ability to kill Lm when compared to inflammatory macrophages from A mice. This impaired listericidal activity of peritoneal macrophages in A mice could be due to a greater proportion of resident macrophages in their inflammatory exudate since they have a lower inflammatory response to stimuli. When homogeneous populations of inflammatory macrophages were compared, no difference was seen in listericidal activity of A and B mice, suggesting that the difference seen with peritoneal inflammatory macrophages was due to a greater proportion of resident macrophages in A than in B mice.

MECHANISMS UNDERLYING DIFFERENCES IN ACCUMULATION OF WHITE BLOOD CELLS AND GRANULOCYTES OF INbred MOUSE STRAINS DURING INFLAMMATION AND INFECTION. W. Smiter, J. Vinckenbosch, A. van der Voort van der Kleij-van Adel, L.F.M. Gemens and F. van Furth, University Hospital, Department of Infectious Diseases, P.O. Box 9600, 3300 PC Leiden, The Netherlands

The difference in natural susceptibility to infection with *L. monocytogenes* between resistant (B10) and susceptible (CBA) mice is reflected in the magnitude of the macrophage inflammatory response (Stevenson, J. Immunol. 1981, 127:401). In the present study we also found a difference between those mouse strains in the accumulation of granulocytes in response to various stimuli in favor of the B10 strain.

Since macrophages regulate the supply of monocytes during an inflammation by secretion and synthesis of factor increasing monocytopoiesis (FIM) which stimulates the production of monocytes in the bone marrow, it seems possible that the difference in inflammatory responses might lie at the production of FIM. We found in the serum of both mouse strains almost the same level of FIM activity. After i.v. injection of B10 and CBA sera containing FIM a monocytosis occurred only in B10 recipient mice; the CBA mice did not respond. This indicates that enhancement of monocytopoiesis during an inflammation depends on a genetically-determined ability of monocyte precursor cells to respond to FIM.

Since the action of FIM is cell-line specific the greater accumulation of granulocytes in the inflammatory exudate of B10 mice cannot be explained by a difference in the response to FIM. It is therefore possible that another factor controls the production and/or release of granulocytes and is responsible for the difference in granulocyte inflammatory response between B10 and CBA mice. An indication for this possibility is that B10 serum can evoke a granulocytosis in B10 mice while CBA serum is negative in this respect.

GENETICALLY-DETERMINED DEFECT IN CHEMOTACTIC RESPONSIVENESS OF INFLAMMATORY MACROPHAGES FROM A/J MICE. M.M. Stevenson, G. Shenouda, D.M.P. Thomson and E. Skamene. The Montreal General Hospital Research Institute, Montreal, Quebec H3G 1A4.

The level of the chemotactic responsiveness of thioglycollate-induced inflammatory peritoneal macrophages in inbred mice is genetically controlled by 2 unlinked, autosomal genes. Among the high responder strains are the C57BL (B)-derived strains, such as, C57BL/6J and B10.A while A/J (A) strain mice exhibit the lowest response. The 3-fold difference in chemotactic responsiveness between thioglycollate-induced inflammatory macrophages from defective A and effective B responder mice was evident to both the complement-derived chemo-attractant C5a and chemotactic lymphokines contained in supernatants of mitogen stimulated spleen cells. In order to characterize the basis of the defect in chemotactic responsiveness of inflammatory macrophages from A mice, we have analyzed some of the biochemical and cellular events leading to migration: 1) at various times through 2 hours following exposure to C5a, approximately 2-3 fold times as many macrophages from B mice compared to A mice became polarized morphologically and 2) C5a-induced membrane hyperpolarization, determined by measuring the transmembrane distribution ratio of ^3H -tetraphenylmethylphosphonium ion (^3H -TPP*), was approximately 3-fold greater in thioglycollate-induced macrophages from B mice compared to cells from A mice. Thus, the low chemotactic responsiveness of inflammatory macrophages from A mice may be due to defects early in the chain of events leading to cellular migration. (Supported by the National Cancer Institute, Canada).

CORRELATION BETWEEN CHEMOATTRACTANT-INDUCED LEUKOCYTE ADHERENCE INHIBITION, MACROPHAGE CHEMOTAXIS AND MACROPHAGE INFLAMMATORY RESPONSES IN VIVO. D.M.P. Thomson, Mary M. Stevenson and Emil Skamene, Montreal General Hospital, Montreal, Quebec, Canada H3G 1A4.

Variations in the magnitude of inflammatory macrophage response in vivo and macrophage chemotaxis in vitro, observed among inbred mouse strains, suggest that these traits are genetically-regulated. The development of an AXB series of recombinant inbred (RI) strains of mice derived from the C57BL/6J (B, high responder) and A/J (A, low responder) resulted in the availability of a large number of new inbred strains which express a spectrum of variations in the magnitude of these traits. These strains were used in the present study as a tool to examine the possible correlation between the phenomenon of leukocyte adherence inhibition (LAI) and those of macrophage inflammatory response in vivo and macrophage chemotaxis in vitro under the assumption that LAI requires the same cellular events as chemotaxis and that LAI resembles, grossly, the accumulation of nonadherent inflammatory cells in vivo. The typing of AXB RI strains for the traits of LAI, macrophage accumulation in vitro and macrophage inflammatory response in vivo resulted in a correlation between the magnitude of response of those 3 phenomena in the total of 19 inbred strains tested, thus suggesting that the chemoattractant-induced LAI is biologically related to the events that mediate macrophage chemotaxis in vitro and the macrophage inflammatory response to sterile irritants in vivo. Supported by a Grant from the National Cancer Institute (Canada) and The Medical Research Council of Canada (Grant # MT-6431).

DIFFERENCE IN INTRACELLULAR KILLING OF *SALMONELLA* TYPHIMURIUM BY GRANULOCYTES OF INBRED MOUSE STRAINS

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The difference in natural susceptibility to infection by *S. typhimurium* between resistant CBA and susceptible C57Bl/10 mice is reflected in the rate of intracellular killing (Kk) of this micro-organism by their resident macrophages (J. Immunol. in press). In this study the function of blood granulocytes and of exudate peritoneal cells (harvested 24 hr after ip injection of 10^3 live *S. typhimurium*) was determined. After in vivo phagocytosis, exudate cells (comprising 78% granulocytes and 20% macrophages for both mouse strains) killed *S. typhimurium* less efficiently than resident macrophages did, but in exudate cells of CBA mice the rate of intracellular killing ($Kk = 0.010 \text{ min}^{-1}$) was twice ($p < 0.02$) that by exudate cells of C57Bl/10 mice ($Kk = 0.005 \text{ min}^{-1}$), which suggested a difference in intracellular killing between the granulocytes of the two mouse strains. Therefore, peripheral blood granulocytes were investigated next. After in vitro phagocytosis of pre-opsonized *S. typhimurium*, the rate of intracellular killing ($Kk = 0.017 \text{ min}^{-1}$) by blood granulocytes of CBA mice was 1.9 times higher ($p < 0.01$) than the value found for C57Bl/10 blood granulocytes ($Kk = 0.009 \text{ min}^{-1}$). These findings suggest that similar differences in bactericidal activities of both granulocytes and macrophages reflect the difference between CBA and C57Bl/10 mice with respect to natural susceptibility to *S. typhimurium*. *L. monocytogenes* were killed with equal efficiency by resident macrophages and exudate cells from both mouse strains ($p > 0.40$), indicating that the findings are specific for *S. typhimurium* and might be relevant for the explanation of the difference in the early phase resistance of inbred mouse strains to this micro-organism.

GENETIC CONTROL OF THE RESISTANCE OF MICE TO SALMONELLA ABORTUS OVIS. F. Lantier and R. Boivin, Station de Pathologie de la Reproduction, INRA, Centre de Tours, 37380 Nouzilly, France.

Genetic control of resistance to Salmonella abortus ovis, a pathogen specific for sheep and goats that induces abortion and, to a lesser degree, mortality of young, was studied with a previously described murine model (Lantier et al., 1981, 1983). LD₅₀ or kinetics of bacterial multiplication in spleen and liver after subcutaneous inoculation in the left hind footpad allowed us to classify C57B1/6 and Balb/c mice as "susceptible" and CBA, C3H/He and DBA/2 mice as "resistant" to S. abortus ovis. This pattern suggests the first week of S. abortus ovis infection is controlled by the Ity gene, as known for other serotypes of Salmonella (Plant and Glynn, 1979). Control by a single gene of the S. abortus ovis multiplication in spleen and liver was confirmed by genetic analysis of F₁, F₂ and Backcross populations resulting from Balb/c x CBA or C57B1/6 x DBA/2 crosses, and by development of a congenic line. However, expression of the Ity gene was not detected in the left popliteal lymph node, and evidences were obtained of other genes influencing the degree of natural resistance to S. abortus ovis. Effect of a low-virulence vaccinal strain of S. abortus ovis was then studied in Ity^S (C57B1/6 and Balb/c) and Ity^R mice (CBA and DBA/2). The Ity gene did not seem to control in vivo survival of vaccinal bacteria during the first week after vaccination, but afterwards elimination of low virulence salmonella was faster in Ity^R lines. Live vaccine induced a 2 log₁₀ protection against subcutaneous challenge with a virulent strain of S. abortus ovis in Ity^R or in Ity^S mice, as well. Genetic control of resistance to S. abortus ovis is now under investigation in the ovine species.

IMMUNE RESPONSES DURING INFECTION WITH A TEMPERATURE-SENSITIVE MUTANT OF SALMONELLA TYPHIMURIUM IN SUSCEPTIBLE AND RESISTANT MICE. Charles Nauciel, Moncef Guenounou, Marianne Deschênes and Esthel Ronco, Université Paris V and Institut Pasteur 75015 PARIS.

Susceptible mice are rapidly killed by virulent strains of S. typhimurium. With a temperature-sensitive mutant of S. typhimurium a long lasting infection could be established in susceptible (C57BL/6) and resistant (A/J) mice. In C57BL/6 mice a large splenomegaly developed and the elimination of bacteria from the spleens was slower than in A/J mice. The proliferative response of splenocytes to B and T cell mitogens and the capacity to mount a delayed type hypersensitivity to sheep red blood cells was strongly suppressed in infected C57BL/6 mice, whereas only a slight and transient suppression was observed in A/J mice. Delayed hypersensitivity to Salmonella antigens was present in both mouse strains. Increased resistance to surinfection with S. typhimurium or Listeria monocytogenes was present in both mouse strains, and appeared with the same kinetics. Thus the depression of some immune responses was predominant in the susceptible mouse strain but did not prevent resistance to reinfection.

MICE WITH EARLY AND LATE GENETIC DEFECTS IN IMMUNE RESPONSES TO SALMONELLA TYPHIMURIUM CAN BE PROTECTED BY A LIVE AVIRULENT VACCINE. Eleanor S. Metcalf, Debra Weinstein, Maryanne Gaffney, and Alison D. O'Brien. Uniformed Services University of the Health Sciences, Bethesda, MD. 20814.

Recent studies have indicated that the expression of several distinct host genes determines whether a mouse will survive challenge with the Gram negative organism, Salmonella typhimurium, which causes a typhoid-like disease in mice. To date, at least four susceptibility genes have been identified, and these genes appear to act at different phases of the infectious process. The early phase is regulated primarily by macrophages, whereas the late phase primarily involves specific antibody formation and cell-mediated immune mechanisms. In the present study, we have analyzed the immune responsiveness of two mouse strains which are susceptible to S. typhimurium strain TML (TML) due to the expression of different genetic loci. C3H/HeJ mice express the Lps^d allele, and die early after infection with TML, whereas CBA/N mice express the xid gene and succumb late after TML infection. C3H/HeJ mice die presumably because of a macrophage defect while CBA/N mice have an antibody-mediated defect. The results of our study show that both C3H/HeJ mice and CBA/N mice make a defective IgG antibody response to the live, avirulent S. typhimurium vaccine SL3235. Nevertheless, both strains are protected from challenge with virulent TML after vaccination with SL3235. Clearance studies of live, virulent TML in SL3235 vaccinated mice demonstrate that no virulent TML are present after day 3 of challenge. Taken together, these results suggest that SL3235 is an effective macrophage activating agent, which acts early to clear all the TML. Thus, late defects in responsiveness can be overridden by an effective early host response and imply that the efficacy of vaccines need rely on the successful and sustained activation of only one arm of the immune response. Supported by NIH grants AI-17755 and AI-17754.

DIFFERENTIAL RESISTANCE TO DISTINCT PATHOGENS
IN HIGH AND LOW RESPONDER LINES OF MICE SELECTED
FOR SALMONELLA ANTIGENS. Osvaldo A. Sant'Anna,
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High(H_{III}) and Low(L_{III}) responder lines of mice obtained by bidirectional selective breeding for quantitative antibody production to flagellar antigens of Salmonella (Selection III), were evaluated for natural and vaccination induced resistance to distinct infections: Rabies virus, Salmonella typhimurium, Schistosoma mansoni and Toxoplasma gondii. The antibody responsiveness to these pathogens are significantly higher in the High than in the Low line. The H_{III} line was more resistant than the L_{III} line for S.mansoni and T.gondii and after vaccination for Rabies virus. On the contrary, the L_{III} line was more resistant than the H_{III} for S.typhimurium. It must be stressed that until now no differences were found in the macrophage activity of these two lines.

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ELEVATED CLASS I H-2 D EXPRESSION ON IMMUNOGENIC VARIANTS OF A SPONTANEOUS MURINE CARCINOMA.

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Both immunogenic and non-immunogenic variants were derived from a recently isolated non-immunogenic CBA/J spontaneous mammary adenocarcinoma following treatment with the mutagen ethylmethane sulfonate (EMS) or the DNA hypomethylating agent and gene inducer 5-Azacytidine (5-Aza-CR). Immunogenic and non-immunogenic subpopulations were characterized by cloning and subsequent in vivo challenge experiments using recipient normal syngeneic CBA/J mice and T-cell deficient BALB/c nude mice. Immunogenic variants were successfully isolated only after drug treatment of the original tumor indicating that if immunogenic variants were present in the untreated tumor line, they existed at relatively low frequency. Since rejection of immunogenic variants, and lymphocytic infiltration of tumor undergoing rejection, appeared to be T-cell dependent processes (ie. absent in nude mice), immunogenic and non-immunogenic clones were compared with respect to various immunological parameters including expression of major histocompatibility complex (MHC) gene products. Our observations can be summarized as follows: first, with some exceptions, most immunogenic variants expressed increased levels of class I H-2 D^K relative to non-immunogenic counterparts or the original tumor line. Second, two immunogenic variants isolated after 5-Aza-CR treatment became increasingly tumorigenic in normal hosts after 6-8 weeks in culture; a reversion paralleled by a phenotypic loss of H-2 D^K. Taken together these observations support and provide a new perspective on the hypothesis that -in some cases- neoplastic cells may be poorly immunogenic as a consequence of low MHC expression.

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GENETIC CONTROL OF RESISTANCE TO THE 402AX TERATOCARCINOMA: REGULATION OF MHC ANTIGEN EXPRESSION BY A SOLUBLE SERUM SUBSTANCE.

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MD 21228 USA.

Resistance to an intraperitoneal (i.p.) challenge of the 402AX teratocarcinoma (129 derived, H-2^b) is controlled by two recessive genes. One gene maps to the H-2IA subregion of the mouse MHC; the second gene maps to the H-3 to H-13 region on mouse chromosome 2. When cultured in vitro or when passaged in vivo in genetically susceptible hosts, the tumor cells do not express MHC class I antigens. However, when passaged i.p. in genetically resistant hosts, the tumor cells are induced to express their own genotype MHC class I antigens. In vivo MHC antigen induction is under the control of the host's immune system. In the present studies, tumor cells cultured in vitro in medium supplemented with 10% serum from genetically resistant, tumor primed mice (B10.SM [H-2^k] or C57BL/6 [H-2^b]) are induced to express MHC class I H-2 antigens. Onset of MHC class I antigen expression on the tumor cells requires 2-3 days co-culture in serum. Serum from genetically susceptible, or unprimed resistant mice has no effect on tumor cell MHC antigen expression. Gamma-interferon co-culture and vesicular stomatitis virus cytopathic assays suggest that the soluble factor regulating 402AX MHC antigen expression is not gamma-interferon. These experiments suggest that MHC class I antigen expression on 402AX teratocarcinoma cells is under genetic control, and is regulated by a soluble, non-gamma-interferon substance contained in the serum of resistant host mice. Supported by NIH CA34368, ACS FRA 251, and MCP/ACS-174-A-1182-19.

EXPRESSION OF $\beta 2$ MICROGLOBULIN-ASSOCIATED MOLECULES IN MURINE LEUKEMIA VIRUS-TRANSFORMED, H-2 CONGENIC TUMOR CELL LINES. Karen K. Klyczek, Brett T. Spear, and Kenneth J. Blank. Department of Pathology, University of Pennsylvania School of Medicine, Philadelphia, PA 19104.

An association between H-2^k haplotype expression and increased susceptibility to murine leukemia virus-induced malignant disease has been observed. Mice expressing the H-2^b or H-2^d haplotypes are relatively resistant. The mechanism of this linkage is unknown. We examined the expression of H-2 class I and other $\beta 2$ microglobulin-associated molecules on the surfaces of Gross murine leukemia virus-transformed tumor cell lines derived from H-2 congenic mice. Some H-2^k tumor cells apparently cease expressing the 45,000 dalton H-2K- or H-2D-encoded class I molecules, as measured by immunoprecipitation with specific antibodies. These cells instead express 50-60,000 dalton $\beta 2$ microglobulin-associated molecules not found on normal cells. Tumor cells derived from H-2^b or H-2^d mice, however, continue to express normal class I proteins. Cytotoxic T cells generated against normal H-2^k cells do not lyse H-2^k tumor cells, while those generated against H-2^k tumor cells do not lyse normal cells or tumor cells from mice expressing other H-2 haplotypes. The loss of normal class I molecule expression and the appearance of unique tumor cell proteins associated with $\beta 2$ microglobulin may be related to the increased susceptibility of H-2^k mice to Gross virus-associated disease.

MACROPHAGE FUNCTION AND IMMUNE RESPONSE OF BRUCELLA ABORTUS NATURALLY RESISTANT & SUSCEPTIBLE CATTLE. Harmon*, BG, Templeton*, JW, Crawford**, RP, Williams***, JD & Adams*, LG. Departments of Veterinary Pathology*, Vet. Public Health** & Vet. Microbiology***, College of Vet. Medicine, Texas Agricultural Experiment Station, Texas A&M University, College Station, TX 77843

Two groups of cows were assembled post-challenge for genetic studies of natural resistance to Brucella abortus S2308. The cross-bred (Bos taurus X Bos indicus) cows were obtained from western Texas which has a low brucellosis incidence & S19 vaccination is not practiced. The 6 mo. old heifers were tested monthly for anti-brucella antibodies by the card, rivanol, complement fixation, hemolysis-in-gel & ELISA tests with uniform negative results, which indicated non-exposure to brucella. The cows were bred & conjunctivally challenged with 10^7 S2308 CFU at mid-gestation, with blood being collected weekly & monthly for serology & lymphocyte blastogenesis respectively. The cows were divided into one group of 12 that had normal term pregnancies & negative culture results for brucella from lacteal & vaginal secretions & placenta, & their calves had negative meconium cultures. Another group of 12 cows all aborted & had positive brucella culture results from lacteal & vaginal secretions or placenta while their fetuses were culture positive for brucella from meconium. An analysis of antibody response to brucella & macrophage function was done retrospectively after the groups were formed. The resistant cows all had low titer short-lived antibody (primarily IgM) responses. The susceptible cows all had long-term high titer antibody responses that was IgM & IgG. The mean blast transformation stimulation index (SI) to irradiated S2308 whole cells of the resistant group was 7.0 & the mean SI was 30.0 for the susceptible group at 15 weeks post challenge. Both groups were BoLA and red blood cell group serotyped & there was not an apparent MHC or blood group association with natural resistance. Respiratory burst (chemiluminescence) of mammary gland macrophages from the resistant group was significantly higher than the susceptible group when challenged with aggregated IgG.

GENETIC REGULATION OF RESISTANCE OF INBRED MOUSE STRAINS TO EXPERIMENTAL MURINE TULAREMIA. Lawrence S.D. Anthony, Emil Skamene and Patricia A.L. Kongshavn, Department of Physiology, McGill University, and the Montreal General Hospital Research Institute, Montreal, Quebec.

We have been investigating the genetic control of resistance to experimental tularemia, caused by the live vaccine strain of *Francisella tularensis*, in inbred mouse strains. C57BL/6 (B6) and A strain mice were infected intravenously with approximately 10^2 viable *Francisella* organisms, and the number of *Francisella* recovered from their livers and spleens determined 2, 5 and 8 days later. Two days following infection, it was observed that the number of *Francisella* in the tissues of A mice was slightly greater (2-10 times) than the number in the tissues of B6 mice. By day 5 post-infection, however, B6 mice were shown to be as much as 100 times more resistant than A mice. Eight days following infection, both strains were observed to be clearing the infection, but A mice were still at least 10 times more susceptible than B6 mice. Using this infective inoculum, some deaths were recorded by day 8 in the group of A mice, whereas none were recorded in the B6 group. A strain survey of 14 recombinant inbred mice derived from A and B6 progenitors was performed, measuring the splenic bacterial counts 5 days following infection. It was observed that 3 strains typed similarly to the A strain and 2 strains typed similarly to the B6 strain. The remaining 9 strains showed a level of resistance intermediate between A and B6. T cell deprivation experiments performed in B6 mice using cyclosporin A indicated that a significant level of T cell-mediated immunity was apparent as early as 3 days following infection. It is proposed that at least 2 genes regulate the resistance of inbred mouse strains to experimental tularemia. The phenotypic expression of these genes is seen best during the phase of acquired cell-mediated immunity to *Francisella* infection. (This work was supported by the MRC of Canada).

HIGHER RESISTANCE OF DBA/2N MOUSE STRAIN TO Yersinia pestis INFECTION. Akira Wake, National Institute of Health, Tokyo, Japan, 141.

After a serendipitous finding that 2 of 5 (40%) male but no female DBA/2N mice could resist to subcutaneous challenge with 130 organisms of Yersinia pestis strain Yreka i.e. a certainly lethal dose for C57BL/6J, C57BL/6N, C3H/HeN, BALB/CJ, BALB/CN, CBA/2N and an outbred DD/S mouse strains, the relationship of this phenotypic resistance to the sex chromosomes of DBA/2N mice was investigated in order to direct the research for elucidating the resistance mechanisms. C57BL/6J, BALB/CJ and DD/S mice were supplied by the Department of Veterinary Medicine, National Institute of Health, Tokyo, and all other mouse strains were purchased from Ohmura Jikkendoubutsu, Co., Japan. F1, F2 hybrid and backcross mice using DBA/2N and BALB/CJ mice were produced in our laboratory. Eleven to 51 male or female mice in each group were subcutaneously challenged with the graded doses of 150, 15,000 and 1,500,000 organisms of a fully virulent Y. pestis strain Yreka and observed for their daily death-survivals as long as 1 month. Because s.c. injection with 200,000,000 organisms of avirulent Y. pestis strains or acetone-killed virulent strains kill all mice within 24h, the survival time of an infected mouse was regarded as the approximate time of in vivo bacterial multiplication counteracting mouse resistance mechanisms. Therefore, not only the percentages of survival mice at the end of experiments, but also statistically significant (parallel line assay) survival-time-prolongations were used as the indicator of resistance. The percentages of resisted mice were as follows: 0% in female and 40% in male DBA/2N; 0% in female and male (BALB/CJ X DBA/2N)F1; 1% in female and male (BALB/CJ X DBA/2N)F2; 0% to 1% in female and 8% in male [(BALB/CJ X DBA/2N) X BALB/CJ] backcross mice against 150 organisms of challenging strain (Yreka). Although all mice were killed by the dose of 15,000 and 1,500,000 Yreka organisms, the male DBA/2N mice showed significantly prolonged survival times. These results suggest that the resistance gene(s) is associated with X-chromosome of male mice and would be expressed more efficiently in the male mice with XY genotype.

SUSCEPTIBILITY TO *E. COLI* URINARY TRACT INFECTION AND LPS RESPONSIVENESS. C. Svanborg Edén and L. Hagberg, Dept. Clinical Immunology, University of Göteborg, Sweden, D. Briles, S. Michalek and J. McGhee Dept. Microbiology Immunology, University of Alabama, Birmingham.

Deficient antibacterial defense mechanisms, have been thought to select the about 3 per cent of children attracting symptomatic urinary tract infection, UTI, from remaining population. Girls with recurrent UTI have an increased susceptibility to epithelial colonization by potentially uropathogenic *E. coli*. Host defects explaining the poor clearance of bacteria which enter the urinary tract have not been identified. This problem was approached experimentally using mouse strains with known defects in antibacterial defense mechanisms. The choice of mice as experimental animals was based on the finding that CBA/J mice retain intravesically injected *E. coli* in kidneys and bladders proportionally to the severity of infection caused by these strains in patients.

The inbred mouse strain C3H/HeJ was shown to be highly susceptible to *E. coli* kidney infection. C3H/HeJ differed from the more resistant mouse strains, including the closely related C3H/HeN mice by their deficient reactivity to lipopolysaccharide, LPS. The susceptibility to UTI was inherited as a codominant trait, as shown by the numbers of highly infected mice in the F₁ (C3H/HeJ x C3H/HeN) and back-cross, F₁ x C3H/HeJ or F₁ x C3H/HeN progeny. The susceptibility of C3H/HeJ mice may be related to the inability of LPS to activate the inflammatory response, since other mouse strains with immune deficiencies (lacking T cell immunity, nu/nu, anti-carbohydrate immunity, xid) or other macrophage defects all showed resistance to UTI comparable to C3H/HeN mice.

DIFFERENCE IN SUSCEPTIBILITY TO GRAMNEGATIVE BUT NOT TO GRAMPOSITIVE URINARY TRACT INFECTION BETWEEN C3H/HeJ AND C3H/HeN MICE. L. Hagberg and C. Svanborg-Edén, Dept. Immunology, University of Göteborg, Sweden, R. and S. Hull, Dept. Microbiology Baylor School of Medicine, Houston, Texas, S. Michalek, J. McGhee, Dept. Microbiology and Immunology, University of Alabama, Birmingham Alabama.

The influence of bacterial properties on the susceptibility to urinary tract infection of C3H/HeJ mice was analysed. Wild type gram-positive and gram-negative urinary isolates (E.coli, Staphylococcus saprophyticus and Streptococcus agalactiae) and Salmonella typhimurium were used for infection. In addition, the role of the O side chain and core structure of lipopolysaccharide was analysed using mutants with R₁ - R₄ cores and S. typhimurium Re. Female C3H/HeJ and C3H/HeN mice were infected intravesically. The bacterial persistence in kidneys and bladders 24 h and 4 days after infection was tested by viable counts on homogenized kidneys and bladders. A difference in clearance from kidneys and bladders between C3H/HeJ AND C3H/HeN mice was found only for LPS containing bacteria. Staphylococcus saprophyticus and streptococcus agalactiae were recovered in essentially equal numbers from both mouse strains. In contrast both E.coli and S. typhimurium persisted in higher number in the kidneys of C3H/HeJ than in C3H/HeN mice. Variations in the O side chain did not eliminate this difference. E.coli Hu734, 075⁺K5⁺ and rfb⁻ mutant 075⁻K⁺ remained in similar numbers in C3H/HeJ mice, although 075⁻K5⁺ was eliminated more rapidly in C3H/HeN mice. The rfb mutants with R₁-R₄ cores and S. Minnesota Re were eliminated after 24 h from the C3H/HeN mice, but remained in significant numbers in the kidneys of C3H/HeJ mice. Thus the bacterial persistence in each mouse strains was related to the overall virulence of the infecting strain with a fairly constant difference between C3H/HeJ and C3H/HeN mice. The results suggest a role of lipid A-induced host defense mechanisms for clearance of gramnegative bacteria from the kidneys.

EVIDENCE FOR SEPARATE GENETIC DEFECTS IN C3H/HeJ AND C3HeB/FeJ MICE THAT AFFECT SUSCEPTIBILITY TO GRAM-NEGATIVE INFECTIONS. Lars Hagberg and Catherina Svanborg-Edén, Dept. Clinical Immunology, University of Göteborg, SWEDEN, David Briles, Dept. Microbiology and Immunology, University of Alabama in Birmingham.

Past studies have suggested a linkage between susceptibility to *Salmonella typhimurium* infection and the *Lps*^d genotype in C3H mice. Recently, this linkage was questioned by finding that C3HeB/FeJ mice (*Lps*ⁿ, *Lps*ⁿ) were highly susceptible to systemic *S. typhimurium* infection. The present study shows a marked difference between C3H/HeJ and C3HeB/FeJ in their susceptibility to gram-negative urinary tract infection. The number of *E. coli* and *S. typhimurium* recovered from the kidneys 24 h after infection was 70-100 times higher in C3H/HeJ than in C3HeB/FeJ or C3H/HeN mice. Subsequently, in C3HeB/FeJ mice *S. typhimurium* multiplied to the level of C3H/HeJ mice, resulting in a shorter mean survival time of C3H/HeJ and C3HeB/FeJ compared to C3H/HeN mice. In contrast, *E. coli* remained localized to the urinary tract of C3H/HeJ mice but were eliminated from C3HeB/FeJ and C3H/HeN mice. Thus, experimental *E. coli* urinary tract infection appears to provide a method to differentiate the genetic defects of C3H/HeJ and C3HeB/FeJ mice. The results support an influence of the *Lps* genotype of clearance of gram-negative bacteria from the kidneys of C3H mice.

Ascending UTI with *E. coli* Hu734

Log bacterial recovery (Mean±SD)						
	No of mice	1 day	No of mice	7 days	No of mice	28 days
C3H/HeN	10	2.41±0.86	9	1.08±1.68	10	0
C3HeB/FeJ	10	2.20±1.12	15	1.01±0.88	10	0
C3H/HeJ ^b	13	4.37±0.56	8	4.05±0.74	9 ^{a)}	2.69±0.50

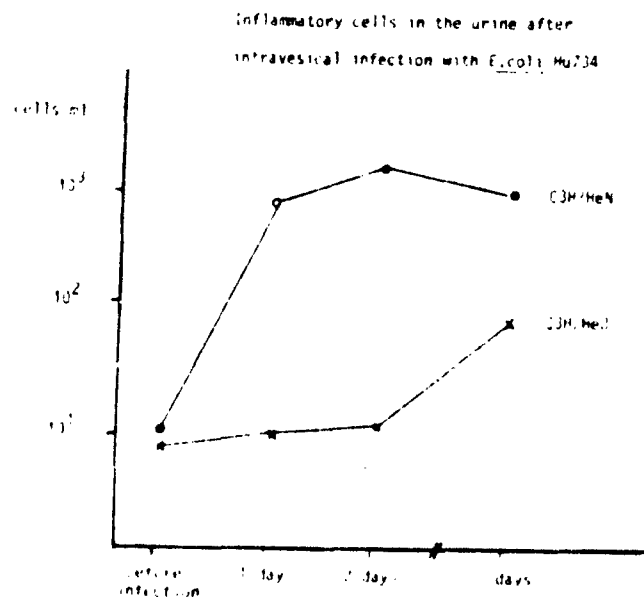
a) One animal had proteus in the kidney and was excluded.

b) C3H/HeJ have significantly higher bacterial recovery than C3H/HeN and C3HeB/FeJ mice at days 1, 7 and 28 ($p < 0.001$).

DEFICIENT URINARY WHITE CELL EXCRETION IN C3H/HeJ COMPARED TO C3H/HeN MICE. C.Svanborg Edén, L.Hagberg, Department of Clinical Immunology, University of Göteborg, Sweden.

C3H/HeJ mice (Lps^d , Lps^d) have an increased susceptibility to urinary tract infection with gram-negative bacteria compared to C3H/HeN and C3HeB/FeJ mice (Lps^n , Lps^n). The resistance to the lethal effects of endotoxin of C3H/HeJ mice was previously shown to be accompanied by an increased influx of peritoneal leucocytes. The aim of this study was to compare the urinary leucocyte excretion in Lps^d and Lps^n C3H mice. Female mice were infected intravesically with *E.coli* Hu734. Urine was collected from individual mice before infection and 4 h, 1, 2, 3 and 7 days after infection.

The number of cells/ml was counted in a hemocytometer chamber. In the C3H/HeN mice, leucocyte excretion started 4 h after infection and decreased after day 3. In contrast the C3H/HeJ showed a slower increase in urinary leucocytes and never reached the levels initially seen in C3H/HeN. These results suggest that the recruitment of inflammatory cells to the urinary tract is deficient in C3H/HeJ mice in spite of the high number of bacteria persisting in the kidneys.



MULTIGENIC REGULATION OF NATURAL RESISTANCE OF THE MOUSE CORNEA TO PSEUDOMONAS AERUGINOSA INFECTION. Richard S. Berk,¹ Linda D. Hazlett,¹ Michael Potter,² and Kirk W. Beisel.³ Departments of Immunology/Microbiology and Anatomy, Wayne State University, Detroit MI 48201;¹ Laboratory of Genetics, NCI, NIH, Bethesda, MD 20205;² Department of Immunology and Infectious Diseases, Johns Hopkins University, Baltimore, MD 21205.³

Previous studies have indicated that multiple genes control the natural resistance of the mouse cornea to Pseudomonas aeruginosa infection. These investigations were undertaken to determine the location of these resistance loci within the mouse genome. A panel of Balb/c (susceptible) congenic lines, which carry chromosomal segments derived from the DBA/2 (resistant) mouse strain, were examined for their resistance to corneal infection. Mice were intracorneally challenged with 1.25×10^8 CFU of P. aeruginosa at 5-6 weeks of age. The ocular response was macroscopically evaluated over a three to six week period. Several of the BALB/c congenic lines, C.D2.Pep-3, C.D2.Idh/Pep-3, C.D2.Pgm-1, and C.D2.Igh-1 recovered from the corneal infection. Differences in the ocular response were noted among these four lines. Even though all the animals from these four lines rapidly cleared the infection within two to three weeks, they differed in the degree of healing. The C.D2.Pep-3 and C.D2.Idh/Pep-3 lines had a greater capacity for healing the cornea compared to the C.D2.Pgm-1 and C.D2.Igh-1 lines. This indicated that the major resistance gene from DBA/2 may be linked to Pep-3 on chromosome 1. The weaker capacity for healing suggests that the genes linked to Igh-1 and Pgm-1 may play a minor role in resistance to corneal damage. The participation of the Igh-1 gene(s) in the ocular response to P. aeruginosa infection was substantiated by a subsequent study in which two Igh congenic lines, BC8 and CB20, were examined. These data suggested that the resistance genes were located on chromosome 1, 5 and 12 and were linked to the Pep-3, Pgm-1 and Igh-1 genes, respectively. Segregation analyses are presently being done to confirm these data. (This work was supported by PHS grants EY-01935 and EY-02986.)

DISSEMINATED CANDIDOSIS IN THE NUDE MOUSE. Gabriel Marquis, Serge Montplaisir, Micheline Pelletier and Pierre Auger. Université de Montréal, Montreal, H3C 3J7.

The influence of the nu mutant gene on the susceptibility of mice to systemic Candida infection was evaluated by monitoring the following parameters in infected BALB/cN nu/nu and nu/+ animals: survival analysis by genotype and by sex, kidney colony counts per organ and per unit of weight, kidney weight variations during the infection compared with values obtained in uninfected mice, which were matched for age and genetic lineage. Both the mean survival time and the proportion of long term survivors were lower in nude mice. Athymic and euthymic female mice lived longer and their prolonged survival was correlated with accrued yeast pullulation in their kidneys. Although the average growth of the organism per organ was always within a log unit, the number of Candida cells per mg of tissue and the variation in weight at the time of death were found to differ with the genotype of the host and the dose of organisms used for intravenous challenge. Infected athymic mice differed in their organ response as they showed a 38% increase in kidney weights within 14 days of challenge when compared with uninfected animals of the same age. Moreover, the number of Candida cells per mg of tissue in athymic mice was similar to that obtained in euthymic littermates after challenge with an inoculum size 25 times larger. It is concluded that (1) non H-2 genetical factors markedly influence resistance to systemic candidosis, (2) the nu gene determines, in the homozygous animal, changes in organ weight profile and density of organisms per mg of tissue which are unlike those seen in thymus-bearing littermates, (3) based on the accrued susceptibility of nu/nu mice, T-cell dependent mechanisms are likely to contribute to a significant extent to growth-restriction of C. albicans.

NATURAL RESISTANCE TO EXPERIMENTAL DISSEMINATED CANDIDOSIS. Serge Montplaisir, Gabriel Marquis, Micheline Pelletier, Pierre Auger and Wayne S. Lapp. Université de Montréal and McGill University, Montreal, Quebec, Canada. To determine differences in susceptibility 175 naive mice from several inbred strains were infected intravenously with 2.5×10^5 Candida albicans cells and monitored as previously published (Infect. Immun. 47:288,1985) with survival analysis and quantitative culture of the kidneys. The shortest mean survival time (MST) was observed with animals of the BALB/cN strain (8.3 days), while animals of the C3H/HeJ strain had a longer MST (13.9 days) with a very high density of organisms per mg of renal tissue. Mice with the aBCD coat color haplotype (C57BL/6J, C57BL/KsJ) had lower colony counts per unit of weight as well as much longer MSTs (55.7 & 40.4 days) and proportion of long term survivors. DW/+, C57BR/cdJ, BRVR and CBA/N mice showed moderate susceptibility. Additional studies in beige mutant mice revealed that the bg^J and bg^{2J} allelic mutations determine a shorter lifespan and accrued yeast pullulation in the kidneys. These results suggest that the genetic control of host resistance is not associated with the H-2 complex and involves multigenic influences.

MURINE RESISTANCE TO COCCIDIOIDOMYCOSIS IS DETERMINED BY A SINGLE GENE. T.N. Kirkland and J. Fierer, Univ. California San Diego, San Diego, CA, USA.

The resistance of inbred mice to peritoneal infection with the fungus Coccidioides immitis is polymorphic. BALB/c and C57BL/6 female mice are quite susceptible ($LD_{50} < 10^3$ organisms); DBA/2 female mice are resistant ($LD_{50} = 1.8 \times 10^5$). The other strains tested so far are either susceptible with LD_{50} 's $< 10^3$ (C57L, AKR, A/J) or intermediate with LD_{50} 's of 10^3 - 10^4 (C3H/HeN, CBA/J, DBA/1J). Resistance is the dominant phenotype. To investigate the number of genes determining resistance, BcD2F1 x Bc and B6D2F1 x B6 female mice backcross mice and parental controls were infected with C. immitis IP. Resistance was defined by the number of organisms in the lungs at d14 in the resistant parent. 38/88 BcD2F1 x Bc mice were resistant; 16/31 B6D2F1 x B6 female mice were resistant to infection. Another group of BcD2F1 x Bc females was typed for resistance in a survival assay. 30/61 backcross animals died from a challenge which killed all the BALB/c and none of the BcD2F1 mice. In all these backcross experiment the ratio of susceptible: resistant mice was very close to 1:1. Furthermore analyses of seven BXD recombinant inbred strains in a survival study revealed that all strains were either susceptible (4/7 strains >70% mortality) or resistant (3/7 strains <25% mortality) to a challenge dose which killed 90% of the C57BL/6 mice and 10% of the DBA/2 mice. All these results are compatible with a single gene determining resistance to infection. We looked for a second gene influencing resistance by testing the (BALB/cxCBA/J)F1 and (DBA/2xCBA/J)F1 for resistance to infection. The (BALB/cxCBA/J)F1 was no more or less resistant than the CBA/J. The (DBA/2xCBA/J)F1 was as resistant as the DBA/2. Therefore, we have no evidence for a second gene influencing resistance to infection in the intermediate CBA/J. We conclude that murine resistance to coccidioidomycosis is determined by a single gene which may have more than two alleles.

EXPERIMENTAL PARACOCCEIDIOIDOMYCOSIS IN HIGH AND LOW ANTIBODY PRODUCER MICE: EVOLUTION OF THE DISEASE, ITS CORRELATION WITH THE HUMORAL IMMUNE RESPONSE AND THE PATTERNS OF TISSUE LESIONS. Mara Silvia Carvalhaes*, Wilmar Dias da Silva*, Esther G. Birman**, Oswaldo Augusto Sant'Anna***, Paulo A. Abrahamschm*, Thereza Liberman Kipnis*. *Instituto de Ciências Biomédicas-USP, **Fac. Odontologia-USP, ***Instituto Biológico.

High (H/f) and Low (L/f) responder mice selected to their capacity to produce antibody against flagellar antigens of *Salmonellae* sp. were infected ip. with 10^6 L forms of *Paracoccidioides brasiliensis*, strain 18. In H/f mice the mortality was 50%, the splenic index was high at the onset of infection (1.0) decreasing to normal levels after 30 days (0.45), and the antibody titers were 4-5 \log_2 . In L/f mice the mortality was 87.5%, the splenic index was above 0.6, and the antibody titers after 30 days was below 2 \log_2 . In L/f mice, granulomae containing a high number of fungi, epithelioid cells, macrophages and few polymorphonuclear cells were found. In H/f mice focal or diffuse infiltration by mononuclear cells with few or even absence of fungi was seen. The passive transfer of immune ascitic fluid to L/f mice, leads to reduction in the number of granulomae and fungi in the lesions.

EXPERIMENTAL PARACOCCIDIOIDOMICOSIS IN B10.D2n AND B10.D2o COISOGENIC MICE. Kipnis, T.L., Carvalhaes, M.S. and Dias da Silva, W. Dept. de Imunologia-ICB/USP. Ed. Bio III-Cidade Universitária. São Paulo, S.P.-Brazil. 05508.

B10.D2n (C5 sufficient) and B10.D2o (C5 deficient) mice were infected, i.p., with 1×10^6 viable forms of Paracoccidioides brasiliensis, strain 18. The cumulative mortality ratio up to 170 th day postinfection was 69% for the B10.D2o and 100% for the B10.D2n mice. After the 70th day of the infection both the number of granulomae and the number of fungi per granulomae were significantly higher in the liver and in the lungs of the B10.D2n mice. Both, mononuclear and neutrophils are present in the granulomae. Specific antibody titers against P.brasiliensis antigens were similar in both coisogenic lines during the entire period of infection. B10.D2n C5 sufficient mice are more susceptible to the P.brasiliensis infection apparently unrelated with their capacity to produce antibody.

HOST RESISTANCE AND CONTROL OF EARLY PROLIFERATION OF TRYPANOSOMA CRUZI. Thomas M. Trischmann and Paul Nawrocki, Dept. of Immunology and Infectious Diseases, The Johns Hopkins School of Hygiene and Public Health, Baltimore, MD. 21205

An early control of proliferation of T. cruzi in mice occurs as early as the first cycle of intracellular replication of the parasite. The extent of parasite proliferation during this period correlates with host resistance: resistant strains have lower parasitemias compared to susceptible strains. The BXH-2 recombinant inbred strain develops an exceptionally high parasitemia due to an inability to limit early proliferation of T. cruzi following infection. This defect in the BXH-2 strain is controlled by a single locus difference between the BXH-2 strain and each of its parental strains: C3H/HeJ and C57BL/6J. In both cases, the inability to limit parasite proliferation acts like a recessive trait. The loci in the C3H and C57BL/6 strains appear to be identical. A mutation is thus likely to have occurred in the derivation of the BXH-2 strain. The designation Crz has been given to the locus in the BXH-2 strain that is responsible for its failure to control early proliferation of T. cruzi.

BXH-2 mice were also tested for their level of resistance to Leishmania donovani and were typed as susceptible. This is in contrast to the original designation of the strain as resistant. The mutation may have occurred after the original typing and also affected resistance to L. donovani. The defective mechanism in the BXH-2 strain may be of general importance in host resistance to parasites.

Among immunological parameters examined, BXH-2 mice markedly differ from the parental strains in their negligible production of serum interferon 24 hours after infection. Preliminary genetic studies show that a lack of interferon production does not always result in a loss of control of early parasite proliferation. However, all mice having the early lack of control also lack an interferon response.

TRYPANOSOMA CONGOLENSE INFECTIONS IN A RESISTANT AND A SUSCEPTIBLE MOUSE STRAIN: QUANTITATIVE DIFFERENCES IN THE PRODUCTION OF FACTOR B OF THE ALTERNATIVE PATHWAY OF COMPLEMENT ACTIVATION. H. Tabel, Dept. Vet. Microbiol., Univ. of Saskatchewan, Saskatoon, Sask. S7N 0W0

Female C57Bl/6J (resistant) and A/J (susceptible) mice were peritoneally infected with 800 to 1000 organisms of T. congolense, clone T6012 and observed up to 12 to 18 days post infection. In C57Bl/6J mice the parasitemia reached an initial peak at day 6, then declined and remained low until 15 to 18 days post infection. In A/J mice the parasitemia was not controlled. It was 2x higher than in C57Bl/6J mice at day 6 and 500x higher at day 12. In infected C57Bl/6J mice spleen weights increased in an exponential fashion from day 0 to day 9. At day 6 as well as day 12, infected A/J mice had significantly larger spleens than infected C57Bl/6J mice, 1.6x and 3.3x respectively. In infected C57Bl/6J mice, plasma levels of complement component C3 were elevated at day 6 and decreased after the first peak of parasitemia by about 30% at day 15 and 44% at day 18. Infected C57Bl/6J mice had increased plasma levels of factor B. The increased levels of this proenzyme showed a biphasic pattern: a peak at day 6, a decline after the first wave of parasitemia towards day 12 and another upsurge after day 12. Normal A/J mice had significantly higher plasma levels of C3 and factor B, however, at 6 days of infection plasma levels of C3 and factor B reached significantly higher levels in C57Bl/6J than in A/J mice. Factor B being synthesized by monocytes and macrophages (Miyama et al., 1980. Microbiol. Immunol. 24: 1223; Whaley, 1980. J. Exp. Med. 151: 501) might merely be an indicator of macrophage function. I, however, suggest that monocytes and macrophages in synergy with activated factor B may exert a cytostatic effect on trypanosomes, similar to the reported synergistic cytotoxicity of human monocytes and factor B on xenogeneic cells (Hall et al., 1980. J. Exp. Med. 156: 834) and that this nonimmune mechanism contributes to the control of parasitemia more effectively in the resistant C57Bl/6J than in the susceptible A/J mice.

ANTIBODY RESPONSES INDUCED BY TRYPANOSOME ANTIGENS IN INBRED MICE RESISTANT OR SUSCEPTIBLE TO AFRICAN TRYPANOSOMES. Leslie Ann Mitchell, Department of Biochemistry and Microbiology, University of Victoria, Victoria, B. C., V8Z 2Y2.

Antibody responses were evaluated in inbred mice previously shown to be resistant (C57Bl/6J) or susceptible (A/J) to infections with relatively avirulent trypanosome species, and in B₆AF₁ hybrid mice (also resistant). Mice were immunized with trypanosome internal and variable surface antigens (presented as solubilized whole Trypanosoma gambiense) and titers and the isotype distribution of antibody responses to both internal antigens and the variable surface glycoprotein (VSG) were determined by solid phase radioimmunometric assay. In separate experiments titers and the isotype distribution of the variant-specific antibody response were determined by indirect immunofluoresence in resistant and susceptible mice during primary infections with Trypanosoma congolense and in challenge infections with the same variant following drug-cure. The results of these investigations showed that after immunization with trypanosome antigens or during active infection, resistant (C57Bl/6J, B₆AF₁) mice made relatively strong primary antibody responses of the IgM isotype. The majority of this response appeared to be directed towards the VSG. The IgM isotype also predominated in challenge immunizations or infections. In contrast, susceptible (A/J) mice made little or no anti-VSG antibody during primary immunization or infection. However, these animals were able to mount strong antibody response (primarily of the IgG isotype) when immunized with trypanosome antigens or after multiple challenge infections.

INTERLEUKIN-1 AND INTERLEUKIN-2 PRODUCTION IN RESISTANT AND SUSCEPTIBLE INBRED MICE INFECTED WITH Trypanosoma congolense. Leslie Ann Mitchell, Department of Biochemistry and Microbiology, University of Victoria, Victoria, B. C., V8Z 2Y2.

In vitro production of interleukin-1 (IL-1) by LPS-stimulated adherent peritoneal exudate and spleen cells and interleukin-2 (IL-2) by ConA-stimulated splenocytes were measured in resistant (C57Bl/6J) and susceptible (A/J) mice during the early stages of subacute infections with the African trypanosome, Trypanosoma congolense. Production of IL-1 was severely depressed in both mouse strains as early as 24 hours after intraperitoneal injection of bloodstream trypanosomes. Mixing experiments suggested that despite the presence of indomethacin during incubation, culture supernatants from adherent cells of infected mice contained activity which inhibited thymocyte proliferation in both the costimulation assays used to measure IL-1 and in routine assays. Similarly, in both mouse strains, an early decline in IL-2 activity was observed followed by partial recovery then depression to subnormal levels. These changes in measurable IL-1 and IL-2 activity in infected mice concurred with progressive depression in the spleen cell proliferative response to Con A.

IMMUNE MECHANISMS AND GENETIC CONTROL OF MURINE RESISTANCE TO A TRYPANOSOMA CONGOLENSE. Margaret Pinder, Alrun Van Melick and Francis Fumoux, Centre de Recherches sur les Trypanosomoses Animales, BP. 753 Bobo-Dioulasso, Burkina Faso, West Africa.

The mechanism and genetics of resistance of mice to Trypanosoma congolense was studied using an isolate (Dinderesso/80/CRTA/3) to which C57B1/6 are highly resistant (low parasitemia, self-cure) and BALB/c, AKR, CBA/J, A/J are susceptible (high parasitemia, death). The resistance of C57B1/6 closely parallels that of certain natural hosts (see communication Roelants et al.). Antibody responses to exposed epitopes of the surface glycoprotein of the clone DiNaT 3.1 were measured by complement mediated lysis and compared in C57B1/6 and BALB/c, following infection with \log_{10} 4.0, 5.0 and 7.0 motile organisms. At all doses serum antibodies appeared 4-8 days earlier in C57B1/6 than in BALB/c, but the peak titres were similar. In resistant mice the antibody rise correlated with clearance of parasites whilst in the sensitive strain antibody appeared at the time many mice were dying. The data are consistent with BALB/c requiring a considerably larger dose of live trypanosomes than C57B1/6 to trigger an immune response. Both strains respond with similar kinetics of antibody production following inoculation of \log_{10} 4.0, 5.0 or 7.0 irradiated trypanosomes. During rising parasitemia both strains were suppressed in their in vitro responses to Con A, PWM and allogeneic cells and in their in vivo response to an unrelated trypanosome surface antigen. As C57B1/6 controlled parasitemia, immunosuppression was gradually reversed whilst in BALB/c it worsened. The relative merits of immunosuppression or antigen handling as the mechanism responsible for the delayed response in BALB/c will be discussed. Inheritance analysis of resistance in C57B1/6 and BALB/c using uncloned Dind.3 trypanosomes showed that resistance was a recessive trait controlled predominantly by a single gene (Pinder, Exp. Parasit. 57: 185, 1984). Studies on DiNaT 3.1 also showed recessive inheritance of resistance and similar studies using CBA-C57B1/6 combinations are underway.

NATURAL RESISTANCE TO TRYPANOSOMIASIS IN WEST AFRICAN CATTLE. Georges E. Roelants, Margaret Pinder, Rémy Queval, Francis Fumcux and Thérèse Traoré-Leroux, Centre de Recherches sur les Trypanosomoses Animales (CRTA) BP. 753 Bobo-Dioulasso, Burkina Faso, West Africa.

Two types of cattle are found in West Africa : Bos indicus (Zebu) and Bos taurus (such as Baoulés, Ndamas, Muturus). In areas of low tsetse fly density the majority of Zebus (75%) present lethal infections with African trypanosomes whereas most Taurine cattle survive. About 2/3 of these Taurine cattle survive in areas of high tsetse fly density whereas the remaining 1/3 and the vast majority of Zebus succumb. Trypanoresistance is generally believed to have a genetic element but precise data are lacking. 61 Baoulés have been selected under high tsetse challenge as resistant or sensitive to trypanosomiasis. The resistance of offspring from parents of known resistance/sensitivity status is under study. An investigation of isoenzymes and erythrocyte groups as markers for trypanoresistance showed that Baoulés with the AA albumin phenotype are 6.3 times more likely to be resistant to high fly challenge. Preliminary observations indicate that the mechanism of resistance is due to a rapid high titer antibody production to epitopes exposed at the surface of live trypanosomes, a mechanism similar to that operating in resistant mice (see Pinder et al. communication), a larger study is ongoing. Inductive and effective phases of the immune response may be modulated by immunosuppression, by interference with antigen presentation due to abnormally elevated zinc levels and by trypanolytic factors generated by the oxidation of polyamines. Suppression of peripheral blood lymphocytes stimulation by lectins in vitro appears only in dying animals but suppression of mixed lymphocyte response occurs with the first waves of parasitaemia. Normal seric zinc levels in cattle are \bar{x} 1.00 ppm \pm 0.30, these are within normal values for resistant (\bar{x} 1.10 ppm) but are abnormally high in sensitive (\bar{x} 1.50 ppm) animals. Polyamine oxidase levels are higher in the serum of resistant (0.59-0.20 units/ml) than in sensitive (0.09-0.08 U/ml) animals. Information will be obtained on the genetic control of these various parameters using the offspring mentioned.

GENETIC CONTROL OF SUSCEPTIBILITY TO INFECTION WITH TRYPANOSOMA MUSCULI. Patricia A.L. Kongshavn, E. Skamene and E. Ghadirian, Department of Physiology, McGill University and Montreal General Hospital Research Institute, Montreal, Quebec.

Trypanosoma musculi produces a characteristic, self-limiting infection which lasts for approximately 3 weeks and comprises a growth phase, a plateau phase and an elimination phase. When A/J and C57BL strain mice are inoculated with T. musculi, blood parasitaemia develops earlier and reaches a plateau value which is 100-fold higher in A/J strain mice. The percentage of young and dividing forms is also significantly greater in this strain 3 days post-infection (p.i.), but not thereafter. The elimination phase is similar in both strains. The differences in parasitaemia between susceptible A/J and resistant C57BL mice are thus seen early in infection, presumably before the development of acquired immunity. Genetic analysis of the gene(s) controlling susceptibility to murine trypanosomiasis was carried out in recombinant inbred (RI) mouse strains derived from A/J and C57BL/6 progenitors. The typing method used to determine the trait of susceptibility was measurement of the level of parasitaemia reached during the plateau phase (11 days p.i.) after intravenous injection of 10^4 parasites. Of 16 RI strains tested, 10 were typed as resistant or C57BL/6-like, 2 were typed as susceptible or A/J-like and 4 strains had an intermediate level of resistance. These data are compatible with the hypothesis that the trait of susceptibility to murine trypanosomiasis is controlled by at least 2 genes.

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IMMUNIZATION TO PRODUCE RESISTANCE TO L. BRAZILIENSIS IN MICE. R.M. Gorczynski, Ontario Cancer Institute, Toronto Ontario, Canada M4X 1K9

BALB/c mice infected intradermally at the base of the tail with 2×10^6 promastigotes of cloned L. braziliensis parasites develop a nonhealing cutaneous lesion. Parasites metastasize to the abdominal viscera and the animals die. Spleen cells taken from such animals at 25-35 days post infection can be used to immunize naive recipients such that these latter animals are resistant to deliberate infection. Two populations of spleen cells were identified with this immunizing capacity. These were an adherent spleen cell population, from which viable parasites could be obtained in culture, and a non-adherent (to glass surfaces) T-lymphocyte population. Immunization with this latter population may be understood in terms of manipulation of idiotypic-anti-idiotypic networks in the immune host. Neither population of cells produced immunity in the recipients which could be simply transferred (with spleen cells alone) to further naive animals. However, when avirulent clones of L. braziliensis parasites, selected for an inability to grow at 28°C (but capable of growth at 19°C), were used in a vaccination strategy the following data were obtained. First, no vaccinated mice developed lesions from the avirulent clones used, even at late times (>200 days) post infection. Second, the vaccinated mice were resistant to challenge with virulent clones of the parasite and even showed some cross resistance to virulent clones of L. tropica. Finally, spleen lymphocytes from vaccinated mice could transfer resistance to further naive recipient mice. The effector population in this latter assay was an lyt-1^+ cell.

STUDY OF GENETIC SUSCEPTIBILITY TO CUTANEOUS LEISHMANIASIS IN RELATION WITH HLA, Gm and Km MARKERS. Dominique Barbier, Florence Demenais, Brigitte David, Madeleine Blanc, Jacques Hors and Nicole Feingold, INSERM U. 155, Paris, France.

In mice, it has been demonstrated that susceptibility to cutaneous leishmaniasis is genetically controlled. To search for such susceptibility gene(s) in humans, an epidemiologic and genetic study was undertaken in a community of Hmong refugees from Laos having recently settled in the rainforest of French Guiana. This is a high transmission area of cutaneous leishmaniasis, due to *Leishmania Braziliensis Guyanensis*, transmitted by phlebotomine sandflies. In the population amounting to 677 individuals in 1982, distributed among 39 families, 92 cases of parasitologically confirmed leishmaniasis have been diagnosed since 1977, when the first group arrived.

Beside the analysis of familial aggregation of the disease currently being processed, we investigated if specific determinants of the markers related to the immune response (HLA system, Gm and Km immunoglobulin allotypes) were involved in the genetic susceptibility to the parasite. Two approaches were used : 1. comparison of the marker phenotype distribution in affected and unaffected unrelated individuals to detect possible associations. 2. distribution of parental haplotypes among affected siblings to test whether a susceptibility gene is tightly linked to one of these markers.

204 and 211 individuals distributed among 16 families were typed for HLA and Gm, Km respectively. When the distribution of HLA-A,B,C and D α antigens was compared between 32 affected and 55 healthy, unrelated individuals, a significant decrease of HLA-C7 antigen among leishmaniasis patients was detected ($P=0.01$) ; no other difference was noted. The distribution of Gm and Km markers in 31 affected and 52 unaffected individuals was not significantly different. Furthermore, no interaction between HLA-C7 and other HLA antigens or Gm, Km allotypes was observed using loglinear models. Neither an HLA, Gm or Km-linked susceptibility gene was demonstrated in the informative sets of affected siblings.

GENETIC CONTROL OF SUSCEPTIBILITY TO LEISHMANIA MAJOR:
SEGREGATION OF THE CONTROL OF CUTANEOUS AND SYSTEMIC
DISEASE. Mock, B. A., Fortier, A. H., Hilgers, J.,
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BALB/c mice are susceptible to Leishmania major
infections: these mice develop nonhealing cutaneous
lesions at the site of inoculation, and infections
metastasize to the lymph nodes, spleen and liver after
4-6 weeks. By 10-12 weeks, the infected foot sloughs
off and 80% of the mice die. In contrast, C57B1/6ByJ
and STS/A mice are resistant to L. major; they develop
neither cutaneous lesions nor systemic metastases over a
12 week period. Recombinant inbred strains initially
derived by mating BALB/c with C57B1/6ByJ (CXB) and STS/A
(CXS) mice were typed for their expression of cutaneous
and systemic susceptibility to L. major amastigotes
administered sc in the footpad. Typing of the CXB and
CXS recombinant inbred strains revealed that at least
two genes are involved in the control of L. major
infection. The development of a nonhealing cutaneous
lesion among the various mouse strains is not 100%
concordant with the development of systemic disease.

Characterization of the Genetic Defect of P/J Mice for Lymphokine-Induced Macrophage Antileishmanial Activities. A.H. Fortier, M.S. Meltzer, and C.A. Nacy. Walter Reed Army Inst. of Res. Washington, DC 20307-5100.

Resident peritoneal macrophages from P/J mice fail to respond to lymphokine-rich culture fluids from antigen or mitogen stimulated spleen cells (LK) for intracellular destruction of the protozoan parasite Leishmania major. Macrophage activation for this effector activity is under the control of a single, autosomal, dominant gene: macrophages from F₁ progeny of unresponsive P/J mice bred to responsive C3H/HeN mice all develop microbicidal activity after exposure to LK; 50% of backcross and 75% of F₂ mice are also responsive. P/J macrophages exposed to activation factors in LK separated by size respond to only one (130 kdalton) of 3 activity peaks observed with similarly treated C3H/HeN macrophages. This activity represents only 6% of total LK activity. The 45 kdalton peak, which accounts for greater than 70% of LK activity, fails to induce intracellular killing of L. major in infected P/J macrophages. Cofractionating with this activity peak for macrophage antileishmanial activity is an antiviral activity that can be neutralized with monoclonal abs prepared against recombinant interferon gamma (IFN γ). Recombinant IFN γ itself, at concentrations of up to 100 IRU/ml, fails to induce P/J macrophages to kill Leishmania: 10 IRU/ml recombinant IFN γ is sufficient to induce 90-100% microbicidal activity in C3H/HeN macrophages. To analyze whether P/J macrophages lacked receptors for IFN γ , we absorbed LK from spleen cells, a T cell hybridoma, or a preparation of recombinant IFN γ with macrophages from P/J or C3H/HeN mice. P/J macrophages, while unable to respond to IFN γ for induction of killing mechanisms, effectively absorbed all the intracellular killing activity in the IFN γ containing preparations. The P/J macrophage defect is not the result of an inability to bind the active molecule in LK supernatants, but may be a defect in signal transduction.

STUDIES ON THE GENETICS OF HOST RESPONSES TO INFECTIONS WITH Echinococcus multilocularis IN RODENTS. W.K. Kroeze and C.E. Tanner, Inst. of Parasitology, Macdonald College, McGill University, 21111 Lakeshore Road, Ste. Anne-de-Bellevue, Que. H9X 1C0.

The tapeworm Echinococcus multilocularis causes a multi-locular form of hydatid disease in rodents, which vary in susceptibility to this parasite. Mongolian gerbils (Meriones unguiculatus), cotton rats (Sigmodon hispidus) and C57L/J mice are more susceptible than other strains of mice, including C57BL/6J. Although growth of the parasite was quite variable, studies in hybrid and back-cross mice between C57L/J and C57BL/6J mice have indicated that susceptibility/resistance to E. multilocularis is under complex host genetic control in mice. Preliminary studies suggest that antibody and cellular responses to this parasite are primarily affected by the parasite burden in individual hosts, and that responsiveness is probably not directly attributable to particular loci in the host genome.
(supported by NSERC)

H-2 GENES INFLUENCE THE KINETICS OF LYMPHOCYTE RESPONSIVENESS IN TRICHINELLA SPIRALIS-INFECTED MICE. Debra A. Dougherty, Lucy Gagliardo, Christopher J. Krco, Chella S. David, and Donald L. Wassom, Cornell University, Ithaca, NY, 14853.

It is well established that genes within the major histocompatibility complex (MHC) influence immunity to Trichinella spiralis infections of mice. It has been proposed that H-2 genes influence the kinetics of lymphocyte responsiveness during such infections and that signals generated by activated lymphocytes are responsible, in turn, for activating the effector phase of the immune response. To determine the influence of H-2 genes on the kinetics of lymphocyte responsiveness, we infected H-2 congenic strains of mice with 150-200 L₁ larvae of T. spiralis and harvested mesenteric lymph node cells from these mice on days 6, 9, and 12 postinfection. The cells were cultured in vitro in the presence of Trichinella antigen and proliferation was assessed by determining the amount of [³H]-thymidine incorporated by dividing cells. Lymphocytes from resistant, H-2^q mice (C3H.Q and B10.Q) reached optimal levels of proliferation by day 9 postinfection whereas an optimal response for cells from H-2^k mice (C3HeB/FeJ and B10.BR) was delayed beyond day 12. This difference in the development of responsiveness was seen over a broad range of in vitro antigen concentrations (50-400 ug/ml) and paralleled the rates at which these mice expelled adult worms from the small intestine. These data confirm that H-2 genes influence the kinetics of lymphocyte responsiveness and are compatible with the hypothesis proposed. (This work was supported by NIH grant AI-17079)

SUSCEPTIBILITY AND RESISTANCE IN MURINE GIARDIASIS.

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Previous studies have shown that the duration of infection with G. muris is markedly different among mouse strains. In the present study the response of inbred mice to G. muris was evaluated during both acute and elimination phases of infection. We found that mice which are susceptible to G. muris (A/J, C3H/He) exhibit a short latent period, high cyst output during the acute phase of infection, and longer period of cyst release. In contrast, the resistant B10.A and DBA/2 mice had a longer latent period, lower cyst output during the acute phase and relatively rapid resolution of infection. Male mice were found to be more susceptible to G. muris when compared to female animals. The trait of susceptibility and resistance during both acute and elimination phases of infection was found to be under complex multigenic control, as determined by examination of response of F₁ hybrid mice and backcross analyses. The course of infection with G. muris was also characterized in six recombinant strains derived from susceptible A/J and resistant C57BL/6 progenitors. The characteristics of infection in AB1, AB2 and AB4 recombinant strains were similar to those of susceptible A/J mice. On the other hand, the course of infection in AB6, AB9 and AB17 recombinant strains was similar to that of resistant C57BL/6 animals. The typing of recombinant strains for susceptibility and resistance to G. muris, will allow for mapping of genes which control resistance in murine giardiasis.

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THYMUS DEPENDENCY OF THE HOST RESISTANCE TO INFECTION WITH HYMENOLEPIS NANA (CESTODE) IN THE NATURAL MOUSE AND UNNATURAL RAT HOSTS. Akira Ito, Department of Parasitology, Gifu University School of Medicine, Gifu 500, Japan.

The present work was done to compare the fates of primary and secondary infections of H. nana in congenitally athymic nude mice and rats, using a mouse-adapted strain of H. nana which mature in mice but never in rats, and to discuss the different immunological strategies against parasitic infections. In the natural mouse host: Mice initially given eggs of H. nana became immune to egg challenge at first and then to cysticeroid (cyst) challenge, but in such immunized mice, initially established immunogenic H. nana (which had developed into adults) survived until the worm expulsion response was expressed. These immune responses were all thymus dependent: Thymocyte-reconstituted nude (TC-nude) as well as euthymic CD-1 mice were highly susceptible to both the tissue and lumen phase of the primary infection (which terminated in worm expulsion after short while patency) but resistant to reinfections, whereas nude mice were highly susceptible to reinfections without rejecting the initially established worms at all. In CD-1 and BALB/c mice which expressed immunity against cyst challenge within 15 days of egg inoculation, the worm fecundity was much lower than in dd mice which expressed it within 30-40 days. The fecundity depressed in euthymic and TC-nude CD-1 mice were heightened in nude mice but somewhat lower than in dd mice. Therefore, the fecundity and longevity of H. nana is controlled under thymus-dependent, acquired immunity, but it may be highly variable among mouse strains in which the onset time of immunity (especially against lumen phase) is highly variable. In the unnatural rat host: In rats, H. nana developed into cysts but excysted juveniles were rapidly rejected and never developed into adult worms even in nude rats, except when the rats, either thymus-deficient or not, were treated with corticosteroids during the suspected lumen phase. However, the effect of cortisone promoting adult development in the rat was more evident in nude rats than in TC-nude or euthymic rats. Therefore, in the rat/a mouse strain H. nana system, thymus-independent resistance to the initial lumen phase might be amplified more in euthymic rats by the presence of cortisone-resistant thymocytes.

GENETIC CONTROL OF SUSCEPTIBILITY TO ENTAMOEBA HISTOLYTICA INFECTION IN MICE. E. Ghadirian, E. Skamene and P.A.L. Kongshavn, The Montreal General Hospital Research Institute, Montreal, Quebec, H3G 1A4, Canada, and Department of Physiology, McGill University, Montreal, Quebec, H3G 1Y6, Canada.

A murine model of infection with Entamoeba histolytica has recently been established in our laboratory. A survey of various strains of mice showed differences in susceptibility to E. histolytica infection. Balb/C, NZB/BIN, C3H/HeCr, B10.A, DBA/2 and C57BL/6 had amoebic cecal loads ranging between 10^6 and 10^7 trophozoites and were classed as susceptible whereas A/J, CE, DBA/1 and CD-1 mouse strains had amoebic numbers of less than 10^2 and were characterized as relatively resistant. Gross examination of the ceca of the susceptible mice showed numerous ulcers over the mucosal surface when compared to resistant strains which had slight or no lesions. The same trend was evident in histological studies of the cecal tissues. Examination of F₁ hybrid animals derived from susceptible B10.A and resistant A/J strains of mice showed that susceptibility was dominant over resistance. Segregation analysis of backcross and F₂ progeny derived from the same progenitor strains was compatible with the hypothesis that susceptibility to E. histolytica infection in mice is controlled by a single, dominant gene which has been designated Enh. A recent further study, in which the pattern of susceptibility to E. histolytica infection has been examined in recombinant inbred strains derived from A/J and C57BL/6 progenitor mice, has provided additional evidence in favour of this single gene hypothesis. (Supported by grants from the Medical Research Council of Canada, and the Fonds de la Recherche en Santé du Québec).

THE METHOD OF IMMUNIZATION INFLUENCES THE EXPRESSION OF H-2 GENES IN IMMUNITY TO NEMATOSPIROIDES DUBIUS INFECTIONS OF MICE. F.J. Enriquez, P.C. Sayles, R.H. Cypess, and D.L. Wassom. Cornell University, Ithaca, NY 14853.

H-2 congenic strains of mice were compared for their ability to resist a challenge infection with Nematospiroides dubius. B10.S, B10.Q and B10.M mice, expressing the s, q, and f haplotypes respectively, were resistant to challenge when compared to B10.BR mice expressing H-2^k alleles. However, the magnitude of this H-2 controlled difference was influenced by the immunizing protocol. B10.BR mice were very susceptible to challenge following a 14 day priming infection but developed considerable resistance to challenge when the priming infection was shortened from 14 to 6 days. A 14 day priming infection allows sufficient time for adult worms to mature. In contrast, termination of the infection on day 6 kills worms in the larval stage, before they migrate to the lumen of the gut. These data establish an important role for H-2 genes in the functional immune response to N. dubius and suggest the hypothesis that susceptible strains may be preferentially immunosuppressed. Specifically, suppression may be a stage specific phenomenon, adult worms being necessary for its expression. (This work was supported by NIH Grant AI-18302)

ANTIGENIC RESPONSIVENESS AND KINETICS OF ANTIBODY PRODUCTION DIFFER AMONG INBRED STRAINS OF MICE INFECTED WITH THE MALARIAL PARASITE, Plasmodium yoelii.

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The course of 17XNL Plasmodium yoelii infection differs among inbred strains of mice. Based on parasitemias on day 18 of infection, mice can be divided into 3 groups. Group I (C3H, BALB/c, B10.BR) have cleared the parasites, Group II (NZB, DBA/2, B10.D2, B6 H-2k) have descending parasitemias of 5%, whereas, Group III (AKR, B6, B10, B10.TL) have ascending parasitemias occasionally, resulting in death. Thus we sought to determine if immunologic differences existed during the course of P. yoelii infection in these strains of mice. The kinetics of Ab dormation was followed using an isotype-specific RIA. Results showed that the rate of anti-malarial IgM production was the same in all groups, but that a significant difference in IgG production occurred. Anti-malarial IgG1, IgG2, and IgG3 Abs were detected (RIA titer 1:50) by day 10 in Group I, day 20 in group II, and day 30 in Group III. Thus, a direct correlation between the kinetics of the IgG Ab response and the rate of parasite clearance was observed. To determine if all 3 groups responded to the same malarial Ags, sera describe above were used to immune precipitate 35S-MET labeled parasite antigens. Examination of autoradiographs demonstrated that the majority of Ags recognized by the various strains were the same. However, the mice differed in response to two proteins -m.w. 70,000 and 37,000. By day 11, mice in Groups I and II (except B6 H-2k) had responded to both proteins whereas mice in Group III had not. At day 21, Group III continued to demonstrated a diminished response to the 70Kd, and no response to the 37Kd protein. Thus, the immune response of resistant and susceptible mice differ with respect to these two proteins.

SUSCEPTIBILITY OF INBRED MICE TO NONLETHAL AND LETHAL ISOLATES OF PLASMODIUM YOELII. Peter C. Sayles and Donald L. Wassom, Cornell University, Ithaca, NY 14853.

Nine inbred strains of mice were characterized for levels of susceptibility to the nonlethal, 17x isolate of Plasmodium yoelii. Mice infected intraperitoneally with 10^6 parasitized red blood cells segregated into two groups when percent parasitemia on day ten was used as a criterion. AKR/J, C57L/J, DBA/1J and DBA/2J mice had average parasitemias below 10 percent, whereas Balb/cJ, C3H/HeJ, C57BL/6J, RF/J and SWR/J mice had average parasitemias in excess of 25 percent. Furthermore, mice susceptible to P. yoelii were more anemic than resistant strains of mice. Susceptible (C57BL/6J), and resistant (DBA/2J) mice were then compared for their susceptibility to two lethal isolates of P. yoelii. DBA/2J mice which were very resistant to the nonlethal isolate of P. yoelii were highly susceptible to infection with the YM and 17x1 lethal isolates. In contrast, C57BL/6J mice which were susceptible to the 17x1 isolate of P. yoelii resisted the lethal strains of malaria. These results demonstrate that strains of mice reported to be susceptible to P. berghei and P. chabaudi may be resistant to other Plasmodium species. In addition, since mice which resist infection with nonlethal isolates of P. yoelii are extremely susceptible to infection with lethal isolates of the same parasite species, it is possible that the mechanisms which control levels of susceptibility to murine malaria may be more complex than previously thought.

OXIDATIVE STRESS TOLERANCE OF INBRED MOUSE RED BLOOD CELLS
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The malaria parasite, Plasmodium berghei, grows at different rates in different inbred mouse strains. We are comparing certain functional characteristics of uninfected normal red blood cells from various inbred mouse strains in order to 1) detect correlations between normal red blood cell function and parasite growth rate and 2) document the range of red blood cell function variation from strain to strain to set the stage for subsequent genetic analysis. For example, we have established that red blood cells from different mouse strains are highly yet consistently variable in how well they withstand oxidant stress in vitro. Washed red blood cells are exposed to 5 mM NaPO_4 + 2 mM H_2O_2 + 4 mM NaN_3 (37°C, pH 7.4) for 1 hour. So treated, red blood cells from C57BL/6J show less than 10% hemolysis while BALB/cJ show more than 65% hemolysis. Red blood cells from the F_1 generation (i.e., offspring from a BALB/cJ X C57BL/6J mating) are all resistant to hemolysis the same as the C57BL/6J male parent. Oxidation of membrane lipids parallels these hemolysis results. In other words, the rate and total quantity of malonaldehyde formation is less in the C57BL/6J than the BALB/cJ red blood cells. This difference in oxidative stress tolerance is apparently due to a single autosomal gene with the C57BL/6J allele dominant to the BALB/cJ allele. Currently we are working to establish the presence/absence of a correlation between the capacity of these cells to tolerate oxidative stress and the rate of malaria growth.

CHANGES IN MACROPHAGE FUNCTIONS ASSOCIATED WITH ACUTE P. CHABAUDI INFECTION. A.K. Chemtai, R. Hamers, and P. De Baetselier, Institute of Molecular Biology Paardenstraat, 65, 1640 St. Genesius-Rod, Brussels.

We studied the impact of acute P. chabaudi infection on peritoneal macrophage associated functions in BALB/c (susceptible) C57BL/6J and CRA (resistant) mouse strains. Antigen presentation based on the proliferative responses of T cells derived from recipients of antigen pulsed macrophages revealed a defect at the level of in vivo induction of T cells. Variation in the antigen presenting functions was not associated with known mouse strain resistance profile to P. chabaudi. Analysis of the macrophages for phagocytosis and production of oxygen active species showed no impairment in their intrinsic capacity to be activated. Chemiluminescence responses as measured through both Fc-receptor and C3b-receptor mediated phagocytosis were found unaltered and enhanced when the macrophages were activated in vitro with lymphokines or interferon-gamma.

ON COLONY FUSION IN SEA SQUIRTS, SELF FERTILIZATION IN FLOWERING PLANTS, AND THE "LYTIC KISS" OF NATURAL KILLER CELLS - A COMPARATIVE ANALYSIS OF STRATEGIES FOR SELF-NONSELF DISCRIMINATION. Klas Kärre, Department of Tumor Biology, Karolinska Institute, Stockholm, Sweden.

Self-nonsel self discrimination may in theory operate through two distinct strategies: 1) by positive detection of foreign molecules on cell surfaces 2) by failure to detect self markers. Mammals have evolved adaptive immune systems based on the first strategy. The second principle is operating in defence reactions of certain invertebrates, e.g. in determination of rejection or fusion between colonies of the sea squirt Botryllus (Burnet, Nature 232:280, 1971). Recognition of self markers on somatic cells of an adjacent colony prevents rejection, enabling the colonies to fuse. The same self markers are believed to control fertilization; at the germ cell level, self recognition will inhibit the sperm from reaching and fusing with the egg, thus favouring outbreeding within the species. Several families of flowering plants may have genetically analogous systems for prevention of self fertilization. In these cases, recognition of a self allele of the polymorphic S gene family has been postulated to inhibit formation or growth of the pollen tube. A reinterpretation of the literature on various "natural resistance" phenomena suggests that a defence based on the simple strategy of recognizing the presence or absence of self may have been conserved throughout mammalian evolution. It is proposed that 1) Natural killer cells are effectors in such a defence system, operating by recognition of a self signal that will inhibit triggering and subsequent delivery of the "lytic kiss" after initial target cell binding 2) Hybrid resistance, rapid elimination of allogeneic lymphoid grafts and natural resistance against metastasis may be partly explained as experimental manifestations of this defence 3) The self signals are encoded by MHC class I genes, or dependent on the expression of such genes for optimal recognition 4) Interferon mediated protection from NK-lysis is in part due to enhanced expression of MHC class I genes induced by the interferon. A strategy to critically test and analyse the predicted type of host defence, based on the use of tumor cell variants showing loss of MHC antigen expression, will be presented.

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SPONTANEOUS & INDUCED PRIMARY ONCOGENESIS IN NK DEFICIENT BEIGE MUTANT MICE. T. Haliotis, J.K. Ball, D. Dexter & J.C. Roder, Queen's University, Kingston, Ontario K7L 3N6

Spontaneous tumor development and primary oncogenesis were compared in a large number of NK deficient, homozygous C57Bl/6-bg/bg mice and their NK normal, heterozygous +/bg littermate controls. In a group of 167 retired breeders followed for spontaneous tumors, the probability of survival for mice eventually dying with a tumor was greater for the NK competent, +/bg than the NK deficient, homozygous C57BL/6-bg/bg mice ($p = 0.0019$), although the higher overall incidence of tumors in the bg/bg group (48%) was not significantly different from that in the +/bg group (37%). In the bg/bg group the incidence of tumor death appeared to increase relatively sharply in the 25-29 mo. age bracket compared to the fairly regular increase in incidence observed in the +/bg group. All the spontaneous tumors except two (discovered in +/bg mice) were classified histologically as widely disseminated malignant lymphomas. A total of 73 bg/bg mice injected s.c. with benzo[alpha]pyrene (BP) had a higher overall incidence of tumors (81%) (rhabdomyosarcomas) than 138 +/bg mice (64%) and in the largest group (0.3 mg, $n=85$) the bg/bg group developed tumors, at a higher incidence ($p = 0.01$) and with a shorter latency ($p = 0.025$) than the +/bg group. On the other hand, mice injected with dimethylbenzanthracene or given 4 weekly doses of 160 rads of gamma irradiation showed no difference in overall tumor incidence. In addition, mice injected with various doses of DMBA-induced murine leukemia virus (DMBA-LV) also showed no significant difference in tumor incidence. These results suggest that a partial NK impairment in beige mutant mice early in life may lead to significantly greater rates of death with spontaneous malignant tumors late in life. Some primary oncogenesis treatments (BP) but not others (DMBA, split-dose irradiation, leukemia viruses) cause tumors with a greater incidence and shorter latency in beige mice. The results suggest, but do not prove, that NK cells play a role in surveillance against spontaneously arising, and possibly some types of carcinogen-induced, tumors.

GENETIC VARIATIONS IN NK AND ADCC ACTIVITIES AMONG VARIOUS STRAINS OF RATS. Hiroyasu Fukui and Craig W. Reynolds, BRMP, BTB, DCT, NCI-FCRF, Frederick, MD. 21701.

Large granular lymphocytes (LGL) have been shown to mediate natural killer (NK) and antibody-dependent cell-mediated cytotoxic (ADCC) activities in humans, mice and rats. To reveal a difference between NK and ADCC activities among various strains of experimental animals with distinct genetical background is essential to better understand the NK and ADCC systems. In the present study, lymphocytes from 4 inbred strains and one athymic nude (rnu/rnu) strain of rats were compared with regard to: 1) NK and ADCC activities against YAC-1 and Ab-coated P815 target cells, 2) Percoll density gradient fractionation, and 3) augmentation of NK and ADCC activities by rat α/β interferon (IFN) or OK-432, a preparation of avirulent Streptococcus pyogenes. In all strains tested, both NK and ADCC activities were closely associated with the presence of LGL. The highest levels of NK and ADCC activities were observed in nude rats, with intermediate activities observed in F344 and Lewis rats. In contrast, WF/N rats had intermediate NK but low ADCC activity with normal number of LGL. In addition, Buffalo rats had both low NK and ADCC activities with extremely low number of LGL. Results obtained from Percoll gradients demonstrated NK activity in higher density LGL, but ADCC activity in association with both lower and higher density LGL. ADCC but not NK activity was associated with the frequency of $Fc\gamma R^+$ LGL from each strain. When nylon wool passed cells from both blood and spleen were incubated with either IFN or OK-432 for 18hr, NK activity was augmented in all strains tested. However, significant augmentation of ADCC activity was observed only in the strains with a low frequency of $Fc\gamma R^+$ LGL. This increase in ADCC activity correlated with an increase in the frequency of $Fc\gamma R^+$ LGL. These results indicate that the functional potential of LGL varies among different strains of rats and should allow us to independently examine the development and mechanisms of augmentation of NK and ADCC activities in rats.

NK CELL ACTIVITY IN RECOMBINANT INBRED MICE: SELECTION OF A MODEL USEFUL FOR IN VIVO STUDIES. Suzanne Lemieux,* Yvette Lusignan,* and Emil Skamene.**
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**Montreal General Hospital Research Institute, Montreal, Quebec H3G 1A4.

The study involves a large set of Recombinant Inbred (RI) strains derived by inbreeding the F₂ generation of A/J(A) and C57BL/6J (B6) matings. The NK cell activity of spleen cell suspensions from individual mice belonging to 20 of these RI strains and the 2 progenitors was assayed against ⁵¹Cr-labelled YAC-1 cells at different effector-to-target (E:T) ratios. The mean NK cell activity values were calculated for each strain and then compared to all others at every E:T ratio. By student's t test analysis, 7 significantly different NK level phenotypes were identified. Genes from both progenitors evidently contribute to the control of the level of NK cell activity in this system as 3 of the phenotypes were significantly higher than the one including the B6 progenitor, the parent with the highest NK cell activity. Data best fit a 3 gene model: 2 genes inherited from the B6 parent, control the NK cell activity and 1 gene, inherited from A, apparently has no effect by itself, but can amplify the lytic activity controlled by the other genes. Since the H-2D^d haplotype has been associated with high NK cell activity, we anticipated that the single amplifier gene inherited from A might in fact be linked to H-2 but this was not the case. From the whole set of RI strains, we have selected 7 H-2^a-matched strains, each of which expresses a different NK level phenotype. In vivo clearance of [¹¹¹In]Ox-labelled YAC-1 cells from the lung in these 7 strains correlates perfectly with in vitro splenic NK cell activity against the same target. This model of 7 H-2-matched mice differing in their NK cell activity level will be invaluable in testing the contribution of NK(YAC-1) cells in natural resistance to infection and malignancy.

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POSSIBLE LOCALIZATION OF GENES UNLINKED TO THE H-2 COMPLEX THAT CONTROL NK ACTIVITY OF BXD RECOMBINANT INBRED STRAINS. Gunnar O. Klein, Karolinska Institute, Stockholm, Sweden and Benjamin A. Taylor, The Jackson Laboratory, Bar Harbor, Maine.

The B6D2F1 hybrid was previously found to have higher NK activity than both parental strains which was attributed to the complementation of the H-2D^d associated NKD-gene from DBA/2 by one or several background genes from B6. Twenty-four BXD RI lines on C57BL/6 x DBA/2 background were tested for NK cell activity against the YAC-1 lymphoma.

Eight of the strains were classified as having high NK and sixteen as having low NK activity. The strain pattern was compared to previous known typings at other loci and five regions showed interesting correlations; Ahd-1 on chr. 4, Lyt-2 on 6, KAP on 7, Kfo-1 on 9 and Es-10 on 14. High NK activity was associated with the B6 derived haplotype except for the gene on chromosome 4.

Most of these genes were expressed independently of H-2 but the NK gene on chr. 6 seems to interact with H-2 associated NK genes as it was only expressed in H-2^b strains. The existence of genes that influence NK activity on chromosomes 4, 7 and 9 is partly confirmed by earlier linkage studies of backcrosses by Petranyi and Kiessling (Immunogenetics 2:53, 1975). The chromosome 9 gene was also detected in B6D2F2:s as a linkage of low NK to the dilute locus (GO Klein and K. Mörre, manuscript in preparation).

INHIBITION OF HUMAN NATURAL-KILLER (NK) MEDIATED LYSIS OF K562 WITH PURIFIED DEFINED CARBOHYDRATES AND MONOCLONAL ANTIBODIES. R.M. Gorczynski*, J. Poders*, and L. Harris**, The Ontario Cancer Institute, Toronto, Ontario* and the Department of Radiation Oncology, University of Western Ontario, London, Ontario**.

Human natural killer cells were obtained by Ficoll Hypaque separation of fresh PBL from normal healthy volunteers, or from cloned cells derived from the same individuals and maintained in tissue culture >4 months. Lysis of the NK-sensitive target K562 was studied in a short-term (4 hrs) ^{51}Cr release test or in a long-term (72 hrs) assay. The latter assay used end-labelling with ^3H -thymidine or trypan blue dye exclusion to detect cell death. NK cells themselves or the 48 hr supernatant derived from resting cells with K562 targets were used as lytic agents. Significant inhibition (>50%) of lysis was seen when either a monoclonal antibody detecting antigens of the SNA- family (anti: Gal β 1 \rightarrow 4 (Fucal \rightarrow 3) GlcNAc β 1 \rightarrow 6) or purified oligosaccharides rich in mannose residues were used. Lysis of a ConA-resistant K562 mutant line was not inhibited by the same sugars. Using a two-step ^{51}Cr -release test in which the stages of target cell recognition and subsequent lysis could be independently assessed, our data indicated that in which the inhibition studied was of the recognition stage (effector:target conjugate formation). Indeed, when a panel of sugars were found to inhibit the lysis mediated by a cell-free cytotoxin found in the supernatant of NK cell mixtures of NK and K562 cells, the pattern of inhibition seen was not the same as that seen when whole cells (NK) were used for lysis. These data lend support to the hypothesis that the inhibition studied is not due to inhibition (post recognition) of the activity of a cell-free cytotoxic molecule. Using cloned cells obtained from individual donors data was obtained which suggest that NK cells are a heterogeneous population in vivo, with different recognition capacities (for independent carbohydrate molecules on target cells) inherent to different cells of this lineage.

CORRELATION OF MALIGNANT POTENTIAL LAMININ RECEPTOR EXPRESSION AND SENSITIVITY TO NATURAL CELL-MEDIATED CYTOLYSIS OF SEVERAL MURINE TUMORS. John C. Biserout, Katherine A. Laybourn and James Varani. Dept. of Pathology, Univ. of Michigan, Ann Arbor, MI 48109.

We have investigated the relationship between expression of laminin receptors, malignant potential and sensitivity of various tumor cells to murine natural killer (NK) or natural cytotoxic (NC) activity *in vitro*. 3-methylcholanthrene induced fibrosarcomas selected for high or low malignant behavior were shown to express low or high levels of free laminin receptors, respectively. The low malignant tumors were sensitive to NC (non-adherent, Thyl-, Asialc GM₁-) cytolytic activity while the highly malignant tumors were totally resistant to NC killing. However, all tumor lines were equally sensitive to alloimmune cytotoxic T lymphocytes (CTL) killing. Preincubation of the low malignant tumors (laminin receptor positive) with exogenous laminin enhanced their lung colonizing ability associated with a concomitant reduction in NC sensitivity. Preincubation of the same tumors with fibronectin or thyroglobulin did not alter their malignant behavior or NC sensitivity. Reduced NC sensitivity was due to failure of NC cells to bind to the laminin pretreated targets. Two T cell lymphomas sensitive to NK killing (YAC-1, RL 1) also expressed free laminin receptors while two NK/NC resistant tumors (EL4, P815) did not. Laminin binding to the NK sensitive targets was shown by laminin induced cell-cell aggregation, immunofluorescence and ¹²⁵I-laminin binding. Preincubation of the NK sensitive targets with laminin but not fibronectin dramatically reduced their sensitivity to NK killing due to reduced NK binding. However, laminin pretreatment of tumor targets did not alter their sensitivity to killing by alloimmune CTL regardless of whether the targets did or did not bind exogenous laminin. This suggests NK/NC cells recognize and bind to sensitive tumor cells through unoccupied laminin receptors on the tumor cell surface. Supported by NIH grant CA26132.

INCREASED LYMPHOMA INCIDENCE IN A SEVERELY IMMUNODEFICIENT LINE OF MICE SELECTED FOR MULTIFACTORIAL ANTIBODY RESPONSIVENESS. Denise Mouton, Yolande Bouthillier, Marie-Claire Martyré, Jean-Claude Mevel and Guido Biozzi, ER 060070 CNRS, Institut Curie, Paris, France.

Five bidirectional selective breedings have been carried out in mice for quantitative antibody responses to various natural immunogens: heterologous erythrocytes, bacteria or heterologous proteins. The immunization procedure also differed in the various selections. Each selection produced a high and a low antibody responder line. The interline difference was in all cases due to the additive effect of several independent loci and was also found for responses to many antigens unrelated with the selection antigens (non specific effect). Genetic and immunological characterization of each selection demonstrated important differences, between homologous lines, in the complexity of the genetic control, the phenotypic expression of the genes and the extent of the non specific effect. To improve the high and low characters, crosses between the five high and between the five low responder lines were performed to obtain balanced hybrids populations on which a further selective process was applied. A multifactorial phenotypic character was chosen, based on primary and secondary responses to several antigens. The interline divergence was rapidly amplified. In particular, a severe and general deficiency was obtained in the low line. A marked incidence of lymphomas was noticed in this line: specific mortality occurred from the 6th month of age and reached 60 % of the mice at the 15th month. In the corresponding high line, lymphoma incidence appeared in only a few mice older than 15 months. In all cases, only T cell markers (Thy, Lyt_1 or Lyt_2 antigens) were expressed on cells of spleen, lymph nodes or thymus. At the selection limit, when high and low lines are homozygous at the loci involved in immunoregulation, the analysis of the results in interline F_2 segregant hybrids will permit to estimate the correlation between the degree of immunodeficiency and the risk of lymphoma incidence.

SPONTANEOUS TUMOURS IN MICE GENETICALLY SELECTED FOR HIGH OR LOW IMMUNE RESPONSIVENESS. Vincenzo Covelli and Gino Doria, E.N.E.A., C.R.E. Casaccia, 00100 Roma A.D.

Nearly one thousand mice selected by G. Biozzi for high (H) and low (L) immune responsiveness to natural antigens (Selection I, II, III) or to phytohemagglutinin (PHA) have been followed for their entire life span to examine their pathology at death. The difference in responsiveness between H and L mice of each selection is controlled by several independent loci: 9-11 (Selection I), 2-8 (Selection II), 4-7 (Selection III), 10-19 (Selection PHA). In all selections the genetic control at these loci is not limited to the response to the selection antigen or mitogen but may also influence the immune response to other immunogens. Spontaneous lymphomas exhibit higher incidence and faster development in L mice than in H mice selected for antibody responsiveness to heterologous erythrocytes (Selection I and II) or for mitotic responsiveness to PHA. However, lymphoma incidence is similar in L and H mice selected for antibody responsiveness to *Salmonella* flagellar antigens (Selection III). The results from Selection PHA as well as the lack of consistent correlation between lymphoma incidence and antibody responsiveness favour the role of T cell-mediated immunity as a defence mechanism against the appearance of spontaneous tumours.

HIGHER NUMBERS OF DTH-MEDIATING T CELLS DEVELOPED AFTER IMMUNIZATION OF HIGH AS OPPOSED TO LOW ANTIBODY RESPONDER MICE : POSSIBLE RELATION TO ACCESSORY CELL FUNCTION.

Gilles Marchal, Geneviève Milon, *Denise Mouton, and *Guido Biozzi, Institut Pasteur and *Institut Curie, Paris.

Most antibody responses to conventional antigens like sheep red blood cells (SRBC) involve cooperation between functionally distinct subpopulations : accessory, antigen presenting cells, T helper and B lymphocytes. The selective breeding of High (H) and Low (L) antibody response lines of mice allows studies on quantitative polygenic regulation of these three cell subpopulations. Previous results have shown that the interline differences in antibody responses in H versus L mice relate mainly to the persistence of the antigen in immunogenic form, a function of accessory cells.

The present data show an additive interline difference in the number of antigen-specific T cells following iv. immunization of H versus L mice. These studies were made possible by (a) the development of a quantitative assay of antigen-specific T cells detected through their ability to locally transfer a delayed-type hypersensitivity (DTH), (b) the previous demonstration that the same T cell could both exert a helper function for antibody response and mediate a DTH reaction. Four days after iv. injection of 10^6 SRBC, the number of SRBC-specific T cells was 10 fold higher in the spleens of H responder than in L responder mice. This interline difference was even more pronounced (30 fold) following iv. immunization with 10^9 SRBC. Cell transfer experiments were used to evaluate the possible relation with accessory cell function. Hybrid F1 (H x L) spleen cells were injected iv. together with the antigen (5×10^8 SRBC) into either H or L lethally irradiated recipients. Four days later the number of SRBC-specific T cells recovered from the spleens was 20 fold higher in H than in L mice. Thus, the interline difference in clonal expansion of SRBC specific T cells appeared to be related to difference in radioresistant accessory cell function.

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LINKAGE OF A PREFERENTIAL RETROVIRAL INTEGRATION SITE
PIM-1 TO THE HISTOCOMPATIBILITY COMPLEX IN MICE.

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Pim-1 is a cellular DNA region that frequently reveals rearrangements in virally induced lymphomas, due to virus integration (1). We have mapped Pim-1 to mouse chromosome 17 with linkage to the H-2 complex. We have used Pim-1 as a probe to follow the segregation of restriction site polymorphism in recombinant inbred strains derived from C57BL/6J and DBA/2J (BxDs). The strain distribution pattern indicates linkage to the H-2K gene (2+2 cM). Confirmation for the map position was obtained by using the H-2 congenic strain Bl0.D2, in which the Bam HI restriction fragment of Pim-1 was donated by DBA/2.

There are two possible mechanisms by which viral integration at this site could be leukemogenic: 1. the viral integration may activate irreversibly an adjacent gene that controls lymphocyte proliferation - an oncogene; 2. the viral integration may interfere with the expression of class I transplantation antigen genes. The inhibition of expression of class I genes may play a critical role in the escape of the transformed cells from the surveillance mechanism of the immune system.

The precise site of integration and the effect on expression of H-2 genes is under investigation.

(1) Cuypers, H.T., G. Selten, W. Quint, M. Zijlstra, E.R. Maandag, W. Boelens, P. van Wezenbeek, C. Melief and A. Berns. Cell 37:141-150 (1984).

H-2 RELATED INFLUENCES ON CARCINOGEN INDUCED TUMOR FORMATION IN A VARIETY OF MOUSE TISSUES. L. Oomen, M. van der Valk, P. Demant and P. Emmelot, Netherlands Cancer Institute, Amsterdam.

Our previous studies have shown that multiple genes in the H-2 complex affect differentially the number and growth rate of transplacentally ENU-induced lung tumors in mice. Here we report the H-2 dependent influence on lung and small intestinal tumor development in mice from five H-2 congenic strains on the C57BL/10 background treated with ENU at the age of 15 days. Tumor development in the lung was most pronounced in mice from the strains B10.A and 2R, whereas mice from the strains 4R and B10 are relatively resistant. Strain 5R showed to be intermediate. With respect to tumor development in the small intestine, strain 2R is most susceptible, strain B10.A intermediate and strains 4R, 5R and B10 are relatively resistant, both regarding the percentage of tumor bearing mice as well as the number of tumors per tumor bearing animal. There is also a difference between strains in the distribution pattern of tumors along the small intestine. In strain 2R most tumors are found in the proximal part, whereas in strain 4R the distal part is most affected. Strains B10.A, 5R and B10 are intermediate between these two extremes.

Thus, carcinogen induced tumor development in the lung and small intestine of mice from H-2 congenic strains on the C57BL/10 background is haplotype dependent. The susceptibility of strain 2R and relative resistance of strains 4R and B10 points to an influence of the E-S region on tumor development in both organs. Apart from differences between strains, differences between sexes (males being more susceptible than females) are also found. In case of lung tumors this intra-strain difference is found in strains 5R and B10, and in case of tumors of the small intestine in strains 5R and 4R. No such differences were found in strains 2R and B10.A. These sex-related differences in tumor susceptibility are thus associated with certain H-2 haplotypes. An H-2 related influence on tumorigenesis in other organs (the lympho-reticular system, the liver and the ovaries) is also indicated, but definitive conclusions have to await further statistical analysis.

GENETIC FACTORS IN THE SUSCEPTIBILITY OF MICE TO URETHAN INDUCED PULMONARY ADENOMAS. Alvin Malkinson, Muriel N. Nesbitt, and Emil Skamene — School of Pharmacy, University of Colorado; Department of Biology, University of California at San Diego; Division of Clinical Immunology and Allergy, The Montreal General Hospital.

Mice of the inbred strain A/J are highly susceptible to the induction of pulmonary adenomas by urethan (producing about 20 tumors per mouse with our protocol), while mice of the strain C57BL/6J are resistant (less than 1 tumor per mouse). We have used a series of recombinant inbred (RI) strains derived from A/J (A) and C57BL/6J (B6) to study the inheritance of susceptibility to tumor induction. The strain distribution pattern of susceptibility in the 40 RI strains we tested does not fit a single-locus model for inheritance. The data best fit a three locus model, with one of the loci (which we designate as Pas-1, for pulmonary adenoma susceptibility) having a stronger effect on susceptibility than the other two. Our attempts to define the map position of Pas-1 have not been successful. We have evidence for extensive recombination between Pas-1 and H-2, c-sis, k-ras and c-fes, as well as more than 90 other loci.

GENETICS OF EXPERIMENTAL COLON CANCER IN MICE. David Fleiszer and Emil Skamene, University Surgical Clinic and Montreal General Hospital Research Institute, McGill University, Montreal, Que. H3G 1A4

The objective of this experiment was to determine the mechanism of inheritance of susceptibility (or resistance) to chemically induced colon cancer in mice using recombinant inbred animals. After determining that the progenitors (A/J and C57BL/6J) were different in their susceptibility (number of tumors formed) to dimethylhydrazine we studied 23 AXB/BXA recombinant inbred strains of mice. Each strain received 15 mg/kg of dimethylhydrazine each week for 20 weeks. After a further 8 weeks, complete autopsies were performed, the large bowel opened and the number of tumors measured and counted. A/J mice developed 19.0 ± 1.8 tumors/mouse (mean \pm S.E.) and the C57BL6/J mice developed 1.0 ± 0.3 tumors/mouse. The 23 recombinant strains had mean tumor loads ranging from 0 to 32. There was no clear separation into distinct populations of susceptible or resistant animals but rather a continuous spectrum ranging from very resistant to very susceptible. We conclude that the susceptibility to dimethylhydrazine carcinogenesis in mice, as measured by the number of tumors formed per mouse, depends on several if not many genes.

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